Aortic Intima Media Thickness in Fetuses and Children With Intrauterine Growth Restriction

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OBJECTIVE: To measure aortic intima media thickness and diameter by ultrasonography in fetuses with intrauterine growth restriction (IUGR) and in appropriate for gestational age (AGA) fetuses and in the same children after a mean follow-up of 18 months.

METHODS: This was a prospective study performed between January 2006 and August 2008. Fetuses were classified as having IUGR if the estimated fetal weight was below the 10th percentile and umbilical artery pulsatility index was greater than 2 standard deviations; they were classified as AGA if the estimated fetal weight was between the 10th and 90th percentiles. Abdominal aortic intima media thickness and diameter were measured in each fetus with IUGR and in each AGA fetus at a mean gestational age of 32 weeks. The same measurements were taken in the children after a mean follow-up of 18 months.

RESULTS: Thirty-eight fetuses with IUGR and 32 AGA fetuses were enrolled in the study. Aortic intima media thickness median values were significantly higher in IUGR than in AGA both in utero (1.9 mm compared with 1.15 mm; $P<.001$) and after birth (2.4 mm compared with 1.03 mm; $P<.001$) and were significantly correlated ($P=.018$, $r=0.48$). At 32 weeks of gestation, aortic intima media thickness in fetuses with IUGR was inversely correlated with estimated fetal weight ($P<.003$; $r=-0.58$). Median diameter of the abdominal aorta and blood-flow velocity at 32 weeks of gestation were significantly higher in fetuses with IUGR compared with AGA fetuses (median diameter 4.5 mm compared with 3.6 mm, $P<.001$, blood-flow velocity 42.5 cm/s compared with 23.3 cm/s, $P<.001$). At follow-up, in 25 children who had had IUGR and 25 children who had been AGA, there was no significant difference in median diameter of the abdominal aorta (6.8 mm compared with 7.5 mm, $P=.21$).

CONCLUSION: Aortic wall thickening in fetuses and children with IUGR shows differences with respect to those who were AGA. This may reflect a correlation between impaired growth in utero, Doppler abnormalities, low birth weight, and early signs of vascular dysfunction.

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LEVEL OF EVIDENCE: II

Low birth weight, caused by preterm birth or intrauterine growth restriction (IUGR) or both, is known to be associated with increased rates of cardiovascular disease and non–insulin-dependent diabetes in adult life.[1–3] The fetal-origins hypothesis proposes that these diseases originate through adaptations of the fetus when it is undernourished. These adaptations may be cardiovascular, metabolic, or endocrine, and they may change the structure and function of the body permanently.[4–11]

The mechanisms involved in determining a high vascular risk in fetuses with IUGR are not yet understood clearly, particularly whether adverse events occurring early in intrauterine life result in any vessel abnormalities. Skilton et al[12] describe the ultrasonography-based measurement of abdominal aortic intima media thickness in children as a feasible, accurate, and sensitive marker of atherosclerosis risk.[13–18] In fact, ultrasonography is able to assess early vascular changes that may be linked to atherosclerosis. Infants who had IUGR have a thicker aorta, suggesting that prenatal events (eg, impaired fetal growth) might be associated with structural changes in the main vessels.[12–14] In fact, a postmortem study performed on

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This article is dedicated to Prof. Ermelando Vinicio Cosmi, a great mentor in perinatal medicine and life.

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infants showed that the abdominal aorta was the first site to be involved in the progression of atherosclerosis.[19] Early endothelial dysfunction, impairment of arterial vasodilatory function, and aortic intima media thickness may play an important role in premature stiffening of the aortic vessels, which predisposes these individuals to hypertension, stroke, nephropathies, and metabolic syndrome.[18] However, during the fetal and infant periods, the natural course of aortic intima media thickness still remains unclear.

The aim of this study was to measure by ultrasonography aortic intima media thickness and diameter in fetuses with IUGR and in appropriate for gestational age (AGA) fetuses and aortic intima media thickness in the children after a mean follow-up of 18 months to test the hypothesis of a predisposition to vascular dysfunction in IUGR.

MATERIALS AND METHODS

The study was performed in the University Hospital of Padua from January 2006 to August 2008. Written informed consent was obtained from each woman before enrollment, and the project was approved by the University Hospital Committee for Research on Human Subjects. Two women were part of a multicenter study that did not interfere with the protocol of the present study.[20]

The protocol was designed to study fetuses that had IUGR and those that were AGA. Participants were selected during routine ultrasonographic fetal biometry and Doppler velocimetry in the third trimester of pregnancy. Fetuses were classified as having IUGR if the estimated fetal weight was below the 10th percentile and umbilical artery pulsatility index was more than 2 standard deviations; they were classified as AGA if the estimated fetal weight was between the 10th and 90th percentiles and Doppler velocimetry was normal.

Inclusion criteria at enrollment were singleton pregnancy, gestational age determined from known last menstrual period, and ultrasound dating before 20 weeks of gestation. Exclusion criteria were twin pregnancy; major congenital anomalies; pregnancies complicated by maternal history of cardiovascular disease or endocrine disorders such as diabetes, hypercholesterolemia, preeclampsia, thyroid, and adrenal problems; and clinical chorioamnionitis. Women who consumed alcohol, nicotine, or any medication such as ritodrine and corticosteroids (except for fetal lung maturation) were excluded.

Data concerning women, pregnancies, and deliveries were recorded according to the routine practice of the Department of Obstetrics and Gynecology.

All women underwent ultrasound and Doppler examinations during pregnancy (at least three times in the case of IUGR). In each fetus with IUGR and each AGA fetus, estimated fetal weight and antenatal testing routinely performed were available. Aortic intima media thickness and diameter measurements and aortic blood-flow velocity were determined for each fetus with IUGR and each AGA fetus at a mean gestational age of 32 weeks (range 30 to 34 weeks).

All parameters were measured by high-resolution ultrasound scan using an ultrasound machine equipped with a 3.5- to 5-MHz linear array transducer (Antares, Siemens Medical Solutions, Mountain View, CA). Intima media thickness and diameter were measured in a coronal or sagittal view of the fetus at the dorsal arterial wall of the most distal 15 mm of the abdominal aorta sampled below the renal arteries and above the iliac arteries as previously described[12–14]; gain settings were used to optimize image quality. Abdominal aortic intima media thickness was defined as the distance between the leading edge of the blood–intima interface and the leading edge of the media-adventitia interface on the far wall of the vessel.[14] This vessel was selected because it is reported to be the first involved in the atherosclerotic process, in particular the dorsal arterial wall, which is the most lesion-prone site seen in autopsy samples.[19] Three measurements were taken, and the arithmetic mean aortic intima media thickness was considered for the study (Fig. 1). Aortic diameter was measured at the same level of aortic intima media thickness, from inner wall to the wall edges. All images were taken at end-diastole of

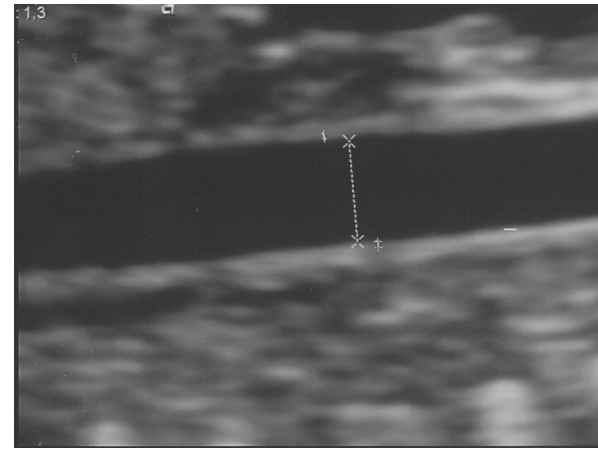

Fig. 1. Ultrasound image showing measurement of aortic intima media thickness and aortic diameter in a fetus.
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the cardiac cycle to minimize the variability. End-diastole was determined as the maximal expansion of the vessel using the cine-loop capability of the ultrasound machine once the images of the entire cardiac cycle were frozen. Blood-flow velocities of the aortic arch were measured using color Doppler velocimetry in the initial portion of the aorta distal to the aortic isthmus. The vessel was visualized in a longitudinal view of the fetus. The transducer was tilted to obtain an angle of insonation as close to 0° as possible and always less than 30°; the high-pass filter was reduced to the minimum. Each measurement was taken during fetal apnea after three consecutive, similar waveforms were obtained. Pulsatility index and time-averaged velocities (defined as the area under the velocity spectral envelope) then were measured using the machine software. The same aortic intima media thickness measurements were performed in the children in a supine position at a mean postnatal age of 18 months.

Fetal examination required no more than 20 minutes, with about 40 minutes required for the children. All the ultrasound studies in fetuses and children were performed by a single, skilled practitioner (E.C.).

Before starting the main research, the intraobserver and interobserver agreement were evaluated in the measurement of aortic intima media thickness. Aortic intima media thickness was measured in 22 AGA fetuses and in 22 children at 18 months. Two practitioners (E.C., V.Z.), blinded among themselves, measured the aortic intima media thickness three times on the same fetus and child after a 2-minute waiting period measured with a stopwatch. Intraobserver and interobserver correlation coefficients were 0.876 and 0.856, respectively.

Statistical analysis was performed using the SPSS 17 software package (SPSS Inc., Chicago, IL). Data are presented as median and range. Abdominal aortic intima media thickness, diameter, and velocity of aortic blood flow were compared between groups using the Mann-Whitney test. Relationships between aortic intima media thickness at 32 weeks of gestation and at 18 months of age and other parameters were studied using the Spearman test. A $P<.05$ was considered statistically significant.

RESULTS

Seventy white women from the Veneto region (Italy) met the inclusion criteria. Among them, 38 had fetuses with IUGR and 32 had AGA fetuses. Anthropometrical and clinical characteristics of the study population are shown in Table 1.

Median maternal age at delivery was 32.1 years (range 19.5–44.7) in the IUGR group and 31.6 years (range 21.2–42) in the AGA group. Twelve women (32%) in the IUGR group delivered vaginally, and 26 (68%) delivered by cesarean. In the AGA group, there were 17 (53%) vaginal deliveries and 15 (47%) cesarean deliveries (12 repeat cesarean deliveries and three

Table 1. Anthropometric, Ultrasonographic Data of the Study Population Before Delivery

	IUGR (n=38)	AGA (n=32)	*P*
Women			
Age (y)	32.1 (19.5–44.7)	31.6 (21.2–42)	.79
Mode of delivery			
Vaginal	12 (32)	17 (53)	.12
Cesarean	26 (68)	15 (47)	.12
Gestational duration (wk)	33 (30–35)	36.7 (33–41)	.001
Maternal smoking	15 (40)	11 (35)	.71
Fetuses			
Abdominal circumference (mm)	280 (249–291)	290 (276–302)	<.001
Estimated fetal weight (g)	1,738 (1,365–2,065)	2,348 (1,930–2,720)	.001
aIMT (mm)	1.90 (1.35–2.37)	1.15 (0.95–1.43)	<.001
Diameter of abdominal aorta (mm)	4.50 (3.66–5.4)	3.60 (2.86–4.24)	<.001
Aortic blood-flow velocity–TAV (cm/s)	42.5 (11.9–89.7)	23.3 (8.7–31.9)	.001
Neonates			
Male	20 (53)	14 (44)	.52
Female	18 (47)	18 (56)	.52
Birth weight (g)	1,830 (1,470–2,310)	3,200 (2,740–3,620)	<.001
Birth length (mm)	418 (389–451)	500 (464–524)	<.001
Abdominal circumference (mm)	280 (263–299)	322 (306.7–333.3)	<.001

IUGR, intrauterine growth restriction; AGA, appropriate for gestation age; aIMT, aortic intima media thickness; TAV, time-averaged velocity.
Data are median (range) or n (%) unless otherwise specified.

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on maternal request). Median gestational age at delivery for fetuses with IUGR was 33 weeks (range 30–35), and median birth weight was 1,830 g (range 1,470–2,310). Median gestational age in the AGA group was 36.7 weeks (range 33–41), and median birth weight was 3,200 g (range 2,740–3,620). There were no differences in maternal age, parity, and mode of delivery between the groups.

Median aortic intima media thickness for fetuses at 32 weeks of gestation was significantly different between fetuses with IUGR (1.9 mm, range 1.35–2.37 mm) and AGA fetuses (1.15 mm, range 0.95–1.43 mm, $P<.001$) (Fig. 2). Moreover, a significant negative correlation was found between aortic intima media thickness and estimated fetal weight at 32 weeks in fetuses with IUGR ($P<.003$, $r=-0.58$), indicating a trend of increasing aortic thickness with severity of IUGR not found in AGA fetuses ($P=.3$, $r=-0.2$).

The median diameter of the abdominal aorta at 32 weeks of gestation was significantly different between the two groups of fetuses (4.5 mm [range 3.66–5.4] compared with 3.6 mm [range 2.86–4.24], $P<.001$). A significant difference was found in median aortic blood-flow velocity (42.5 cm/s [range 11.9–89.7] and 23.3 cm/s [range 8.7–31.9], $P<.001$).

At the time of follow-up, the parents of 25 children who had had IUGR and 25 children who had been AGA agreed to the study. Parents of 10 children who had had IUGR and seven who had been AGA declined. Three children who had had IUGR were moving and crying during the aortic intima media thickness measurements, and follow-up was stopped after 40 minutes. The median body weight of the children who had had IUGR was 12,300 g (range 11,100–13,500), and the median body weight of those who had been AGA was 12,200 g (range 11,200–13,400). Therefore, no significant differences in anthropometric features in the study population were found (Table 2). Median aortic intima media thickness at a postnatal age of 18 months (range 17–21 months) was 2.4 mm (range 1.5–3.1 mm) in the IUGR group and 1.03 mm (range 0.88–1.24 mm) in AGA group. Therefore, aortic intima media thickness was significantly increased in children who had had IUGR compared with those who had been AGA ($P<.001$) (Fig. 3). Moreover, a positive linear correlation was observed between the prenatal aortic intima media thickness values and postnatal aortic intima media thickness ($P<.019$, $r=0.48$) in the children who had had IUGR, which was not found in those who had been AGA. At follow-up, there was no significant difference between median diameters of the abdominal diameter in the children who had had IUGR compared with those who had been AGA (6.8 mm [range 4.2–9] compared with 7.5 mm [range 5.2–9], $P=.21$).

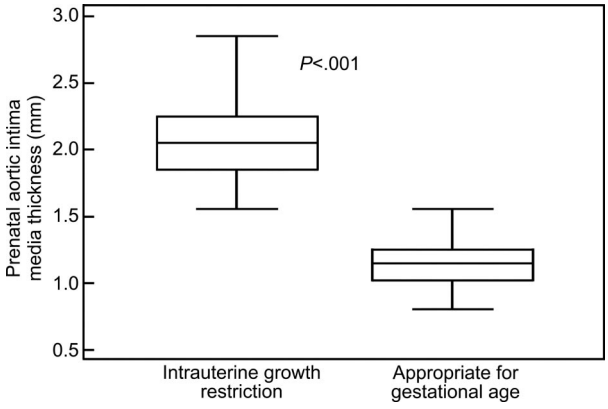

Fig. 2. Difference in aortic intima media thickness measurements between fetuses with intrauterine growth restriction and appropriate for gestational age fetuses. Values are reported in box plot.

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DISCUSSION

The present study shows that aortic wall thickness is significantly increased in fetuses and children with IUGR compared with AGA fetuses and children.

Moreover, aortic intima media thickness measurements in fetuses with IUGR are inversely related to estimated fetal weight, showing that low birth weight and Doppler abnormalities may be correlated with an altered vascular structure causing possible endothelial damage. This is consistent with the finding that atherosclerosis begins to develop first in the intima of the aorta.[19]

This study shows that the assessment of aortic intima media thickness in fetuses and children with IUGR and AGA fetuses and children was feasible and reproducible. There were no cases in which we were unable to obtain the measurement. The intraobserver and interobserver variability demonstrated the effectiveness, simplicity, and reproducibility of the technique. This study demonstrates a noninvasive ultrasound method to evaluate preclinical atherosclerosis in preterm fetuses and children.[12,16,17]

Moreover, this study provides a reliable method to evaluate a marker of atherosclerosis in a longitudinal fashion before and after birth. The study was carried out in the same population, providing the advantage of having enrolled fetuses whose blood flow dynamics were known in utero as well as after delivery. In fact, the fetuses with IUGR in the study

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Table 2. Anthropometric and Ultrasonographic Data of the Study Population at the Time of Follow-Up (18 Months)

Follow-Up	IUGR (n=25)	AGA (n=25)	*P*
Male children	13 (52)	9 (36)	.33
Female children	12 (48)	16 (64)	.33
Body weight (g)	12,300 (11,100–13,500)	12,200 (11,200–13,400)	.76
Length (cm)	85 (79.5–91.5)	85.5 (79–92)	.91
Age (mo)	19 (12.3–24.7)	21 (12.7–27.7)	.63
Child's aIMT (mm)	2.4 (1.5–3.1)	1.03 (0.88–1.24)	<.001
Diameter of abdominal aorta (mm)	6.8 (4.2–9)	7.5 (5.2–9.4)	.21

IUGR, intrauterine growth restriction; AGA, appropriate for gestational age; aIMT, aortic intima media thickness.
Data are n (%) or median (range) unless otherwise specified.

were those with an umbilical artery pulsatility index more than 2 standard deviations compared with fetuses with appropriate growth and normal blood flow dynamics.

Furthermore, these studies classified children as having IUGR without taking into account the cardiovascular status of the fetus before birth, with particular attention on the Doppler evaluation. We know of no report of children who had IUGR or who were small for gestational age that differentiates these two entities resulting in the initial cardiovascular changes in utero; no underlying cause has been demonstrated previously for the resulting cardiovascular disease later in life.

Moreover, the present study shows that the velocity of blood flow through the aortic arch was higher in fetuses with IUGR than in AGA fetuses. We suggest that this is related to a higher cardiac afterload due to increased resistance in the umbilical artery and placental insufficiency.

Nevertheless, previous studies have shown that, in children who had IUGR, aortic intima media thickness was greater in those with the lowest birth weight, suggesting that atherogenesis and an increased arterial stiffness may be a potential mechanism mediating the mentioned epidemiological link between impaired fetal growth and cardiovascular disease in adulthood, similar to major environmental risk factors such as cigarette smoking and hypertension.[12–15] Unlike these studies, which focus on older age groups, our method allows for prospective examination of the effects of impaired fetal growth, without the effect of postnatal confounders, by measuring aortic intima media thickness. We now may evaluate this known marker of endothelial dysfunction and potential arterial health directly in utero from the second to third trimester of gestation and in children.

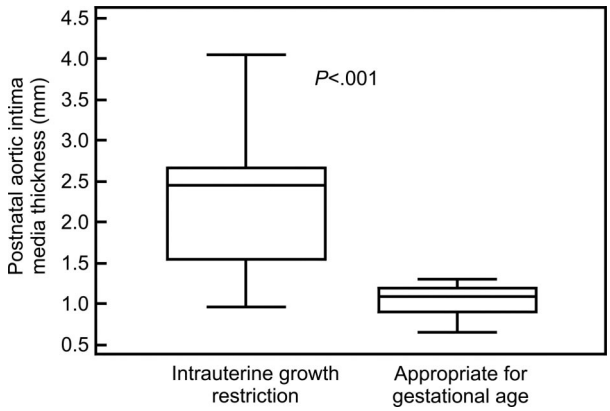

Fig. 3. Difference in aortic intima media thickness measurements between infants who had intrauterine growth restriction and appropriate for gestational ages. Values are reported in box plot.
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Our results are in agreement with previous studies that correlate low birth weight with endothelial damage that may influence arterial function and the overall incidence of cardiovascular events.[17,18] These results suggest that, in addition to other pathogenic mechanisms, an increased arterial thickness probably is present already in fetuses with IUGR from intrauterine life and this, together with other factors such as smoking, fat consumption, and inactivity, could play a role in programming adult disease as previously suggested.[12–14]

Limitations of the present study are the small sample size, studying the same ethnic group, and data that did not account for differences in gender. Although these tests require advanced ultrasound equipment and experience in ultrasound measurements, which are not performed routinely, we believe that such measurements provide a valuable assessment from an early age as to the potential development of cardiovascular disease in adulthood.

In conclusion, we found that, in fetuses and children with IUGR, aortic intima media thickness is increased compared with AGA fetuses and children,

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suggesting that IUGR may represent an in utero marker of potential atherosclerosis development.

REFERENCES

1. Barker DJ. Adult consequences of fetal growth restriction. Clin Obstet Gynecol 2006;49:270–83.
2. Barker DJ. In utero programming of cardiovascular disease. Theriogenology 2000;53:555–74.
3. Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, et al. Developmental plasticity and human health. Nature 2004;430:419–21.
4. Eriksson JG, Forsén TJ, Kajantie E, Osmond C, Barker DJ. Childhood growth and hypertension in later life. Hypertension 2007;49:1415–21.
5. Lawlor DA, Ronalds G, Clark H, Smith GD, Leon DA. Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s: findings from the Aberdeen Children of the 1950s prospective cohort study. Circulation 2005;112:1414–8.
6. Osmond C, Kajantie E, Forsén TJ, Eriksson JG, Barker DJ. Infant growth and stroke in adult life: the Helsinki birth cohort study. Stroke 2007;38:264–70.
7. Osmond C, Barker D. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environ Health Perspect 2000;108(suppl 3):545–53.
8. Strufaldi MW, Silva EM, Franco MC, Puccini RF. Blood pressure levels in childhood: probing the relative importance of birth weight and current size. Eur J Pediatr 2009;168: 619–24.
9. Lawlor DA, Hübinette A, Tynelius P, Leon DA, Smith GD, Rasmussen F. Associations of gestational age and intrauterine growth with systolic blood pressure in a family-based study of 386,485 men in 331,089 families. Circulation 2007;115:562–8.
10. Johansson S, Iliadou A, Bergvall N, Tuvemo T, Norman M, Cnattingius S. Risk of high blood pressure among young men increases with the degree of immaturity at birth. Circulation 2005;112:3430–6.
11. Irving RJ, Belton NR, Elton RA, Walker BR. Adult cardiovascular risk factors in premature babies [published erratum appears in Lancet 2000;356:514]. Lancet 2000;355:2135–6.
12. Skilton MR, Evans N, Griffiths KA, Harmer JA, Celermajer DS. Aortic wall thickness in newborns with intrauterine growth restriction. Lancet 2005;365:1484–6.
13. Koklu E, Ozturk MA, Gunes T, Akcakus M, Kurtoglu S. Is increased intima-media thickness associated with preatherosclerotic changes in intrauterine growth restricted newborns? Acta Paediatr 2007;96:1858.
14. Koklu E, Kurtoglu S, Akcakus M, Yikilmaz A, Coskun A, Gunes T. Intima-media thickness of the abdominal aorta of neonates with different gestational ages. J Clin Ultrasound 2007;35:491–7.
15. Litwin M, Niemirska A. Intima-media thickness measurements in children with cardiovascular risk factors. Pediatr Nephrol 2009;24:707–19.
16. Skilton MR. Intrauterine risk factors for precocious atherosclerosis. Pediatrics 2008;121:570–4.
17. Järvisalo MJ, Jartti L, Näntö-Salonen K, Irjala K, Rönnemaa T, Hartiala JJ, et al. Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. Circulation 2001;104:2943–7.
18. Franco MC, Christofalo DM, Sawaya AL, Ajzen SA, Sesso R. Effects of low birth weight in 8- to 13-year-old children: implications in endothelial function and uric acid levels. Hypertension 2006;48:45–50.
19. McGill HC Jr, McMahon CA, Herderick EE, Tracy RE, Malcom GT, Zieske AW, et al. Effect of coronary heart disease risk factors on atherosclerosis of selected regions of the aorta and right coronary artery. PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. Ateriscler Thromb Vasc Biol 2000;20:836–45.
20. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 2007;109:253–61.

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