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Influence of intrauterine growth status on aortic intima-media thickness and aortic diameter in near-term fetuses: a comparative cross-sectional study

Original Article

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Abstract

Intrauterine undernutrition may lead to fetal vascular programming. We compared abdominal aortic intima-media thickness (aIMT) and aortic diameter (aD) between appropriate for gestational age (AGA) and growth-restricted fetuses (GRF). We recruited 136 singleton fetuses at 34–37 weeks of gestation from Fetal Medicine Unit of Aga Khan University Hospital, Karachi (January–November 2017). Subjects were classified as AGA ($n = 102$) and GRF ($n = 34$) using INTER-GROWTH 21st growth reference and standard ultrasound protocol. Their far- and near-wall aIMT and aD were compared after adjustment of maternal age, first-trimester body mass index, fetal gender, hypertension and hyperglycemia in pregnancy. As the severity of growth restriction increased in GRF, aIMT and aD showed an increasing and a decreasing trend, respectively. Both far- and near-wall aIMT in GRF [(adj. $\beta = 0.082$, 95% confidence interval [CI] 0.042–0.123) and (adj. $\beta = 0.049$, 95% CI 0.010–0.089)] were significantly greater with reference to AGA fetuses. GRF subgroup analysis into small for gestational age (SGA) fetuses and intrauterine growth restricted (IUGR) revealed highly significant difference between AGA and IUGR for far (0.142 mm, P-value < 0.001) and near-wall aIMT (0.115 mm, P-value < 0.001) and marginally significant aD difference (0.51 mm, P-value 0.05). These findings suggest that the extent of fetal aortic remodelling is influenced by the severity of growth restriction. Hence, the targeted interventions for the cardiovascular health promotion of IUGR and SGA born neonates are desirable during early childhood, particularly in set ups with high prevalence of low birth weight babies.

Introduction

According to the developmental origins of health and disease (DOHaD) hypothesis pioneered by Sir David Barker, children born as low birth weight (LBW) are found to have an increased risk of cardio-metabolic diseases later in life as a result of intrauterine adaptation and developmental plasticity.[1] Such intrauterine programming may cause permanent structural and functional changes in their body organs.[2,3] Fetuses with a birth weight below the 10th centile for the gestational age are considered undernourished[4] and constitute 5%–10% of all newborns.[5] These include small for gestational age (SGA) and intrauterine growth-restricted (IUGR) fetuses.

Recently, researchers have shown that children born as undernourished tend to demonstrate altered cardiac functions during neonatal life,[6] infancy,[7] childhood[8] and adolescence,[9] supporting the paradigm of DOHaD. Based on the evidence that the first subclinical atherosclerotic lesion is initiated in the abdominal aorta,[10] Skilton *et al.*[11] and Koklu *et al.*[12,13] observed significantly thicker abdominal aortic intima-media (aIMT) in term-born IUGR neonates compared to those born as appropriate for gestational age (AGA). Similarly, Sehgal *et al.*[6] reported a significantly thicker aortic intima-media in term SGA neonates who had normal antenatal Doppler parameters. However, observation of significant thickening of abdominal aortic intima-media of IUGR fetuses by Cosmi *et al.*[14] and of SGA fetuses additionally by Gomez *et al.*[15] suggest that in a nutritionally compromised *in-utero* environment, subatherosclerotic changes may be initiated as early as in the fetal life.

These previous studies have, however, examined the aortic wall thickness only on the far wall of the abdominal aorta.[16] To the best of our knowledge, no studies have so far carried out measurements of the aIMT on the near wall during fetal life in comparison with far wall adjusting for fetal and maternal characteristics. Assessment of the thickness on the near wall of aIMT would give us an insight into the feasibility for its measurement and whether there is any possible difference in its measurements compared to the far wall. The primary aim of this study was to

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examine the far- and near-wall thickness and the diameter of the distal segment of the abdominal aorta of growth-restricted fetuses (GRF) and to compare these measurements with those of AGA fetuses. Our secondary objective was to assess differences in similar measurements amongst subgroups of GRF, that is, IUGR and SGA with AGA fetuses.

Material and methods

Design

We conducted a comparative cross-sectional study on 136 fetuses [AGA ($n = 102$), GRF ($n = 34$)] seen at Fetal Medicine Unit of the Aga Khan University Hospital, Karachi, from January to November 2017. The study protocol was approved by the Ethical Review Committee (ERC Ref. 4555-CHS-ERC-16). Written consent was acquired from pregnant mothers after informing the study aims and design. We included singleton pregnancies at 34–37 weeks of gestation (late preterm and term period) with or without hyperglycemia in pregnancy (gestational or essential diabetes mellitus)[17] and hypertensive disorders of pregnancy (gestational hypertension, preeclampsia and eclampsia, chronic hypertension or preeclampsia superimposed on chronic hypertension),[18] and excluded multiple pregnancies and fetuses with chromosomal and structural anomalies.

Variables and data collection

Centiles for the estimated fetal weight (EFW) and postnatally confirmed birth weight were determined using INTERGROWTH 21st fetal and postnatal growth reference standards, respectively.[19,20] For subgroup analysis, GRF having birth weight less than 10th centile were further classified into IUGR (birth weight centile <3rd alone or >3rd and <10th + abnormal Doppler studies) and SGA (birth weight centile >3rd and <10th + normal Doppler studies) according to the published guideline.[21] Doppler studies were considered abnormal in one or more of the following conditions: uterine artery pulsatile index (PI) >95th centile, umbilical artery PI > 95th centile, middle cerebral artery PI < 5th centile and cerebro-placental ratio <5th centile.

Data were obtained from the hospital records. Maternal characteristics included age, parity, first-trimester body mass index (BMI) and history of medical disorders of pregnancy such as hyperglycemia and hypertensive disorders. Neonatal characteristics analysed were gender, gestational age (GA) at delivery, mode of delivery, birth weight and admission to nursery or neonatal intensive care unit.

Fetal ultrasound parameters

A high-resolution Medison Accuvix 20 ultrasound machine with a 3.5–5 MHz linear array transducer provided information about GA at ultrasound, head and abdominal circumference, femur length, occipito-frontal and biparietal diameters and estimated fetal weight (EFW). In addition, blood flow studies of uterine, umbilical and middle cerebral arteries were obtained. Image of the fetal abdominal aorta was obtained in a coronal view. The near and far walls of aIMT were defined with respect to the proximity of the ultrasound probe to the vessel wall. aIMT was labelled as the distance between the leading edge of the blood intima interface and that of the media adventitia interface on the near and far wall of the distal 15 mm of the longitudinal segment of the unbranched abdominal aorta just before the bifurcation into iliac arteries.[22] The aortic diameter (aD) was measured between the blood intima interfaces at the same level of aIMT.

Offline analysis

Digitally stored images were analysed offline by manual placement of the callipers on the end-diastolic frozen images. Two independent evaluators blinded to the fetal growth status carried out this analysis three times to reduce information bias and chance error. Reliability of measurements was assessed by Bland-Altman technique for inter-observer reliability. Intra-class correlation (ICC) was considered adequate for intra-rater variability if between 0.5 and 0.7 and as excellent if more than 0.7. An average of the mean recording of both observers was used for the later analysis.

Sample size

Sample size calculations using OpenEpi indicated the need of 34 GRF and 102 AGA fetuses in the ratio of 1:3 to detect a difference of 0.1 mm or more for aIMT amongst the two groups. The calculations were based on 80% power, confidence intervals (CIs) of 95%, far-wall maximum standard deviation of 0.17 mm as reported for term AGA fetuses[23] and included 10% attrition rate based on poor image quality.

Statistical analysis

All continuous variables are presented as median with interquartile range (IQR) except for birth weight, the latter being presented as mean with standard deviations. Categorical variables are reported as frequency and percentages. The normality assumption of all continuous variables was assessed *a priori* by histogram and Shapiro–Wilk test. To compare aIMT and aD between AGA and GRF fetuses and to assess the overall difference of near and far wall between the groups, Wilcoxon rank sum was used. Subgroup analysis comparing aIMT and aD of IUGR and SGA fetuses with AGA was performed using Kruskal-Wallis test. Statistical significance was inferred at $P < 0.05$. Variables having P-value cut-off of 0.25 were assessed for collinearity before proceeding to the stepwise building of a multivariable model. Multiple linear regression was performed to assess the relationship of fetal growth status separately with far- and near-wall aIMT after adjusting for maternal age, first-trimester BMI, fetal gender, hypertensive disorders and hyperglycemia in pregnancy. Data were analysed using Stata version 14 (StataCorp, College Station, TX, USA).

Results

Of the total 144 fetuses enrolled, eight were excluded because their images were not technically suitable for offline analysis. Hence, our final analysis is based on 136 subjects comprising 102 AGA and 34 GRF. The Bland–Altman plot indicated an excellent agreement between the reading of two raters for far wall (mean difference = 0.007 mm, P-value 0.65) and near wall (mean difference = 0.029 mm, P-value 0.71) (Fig. 1a, 1b). After determining high ICC for aIMT (0.84) and aD (0.89), we used the measurements of the most experienced rater for final analysis.

Maternal and Neonatal characteristics (Tables 1 and 2)

Maternal age, parity and hypertension in pregnancy did not differ significantly between GRF and AGA groups. However, hyperglycemia in pregnancy and first-trimester BMI was found to be

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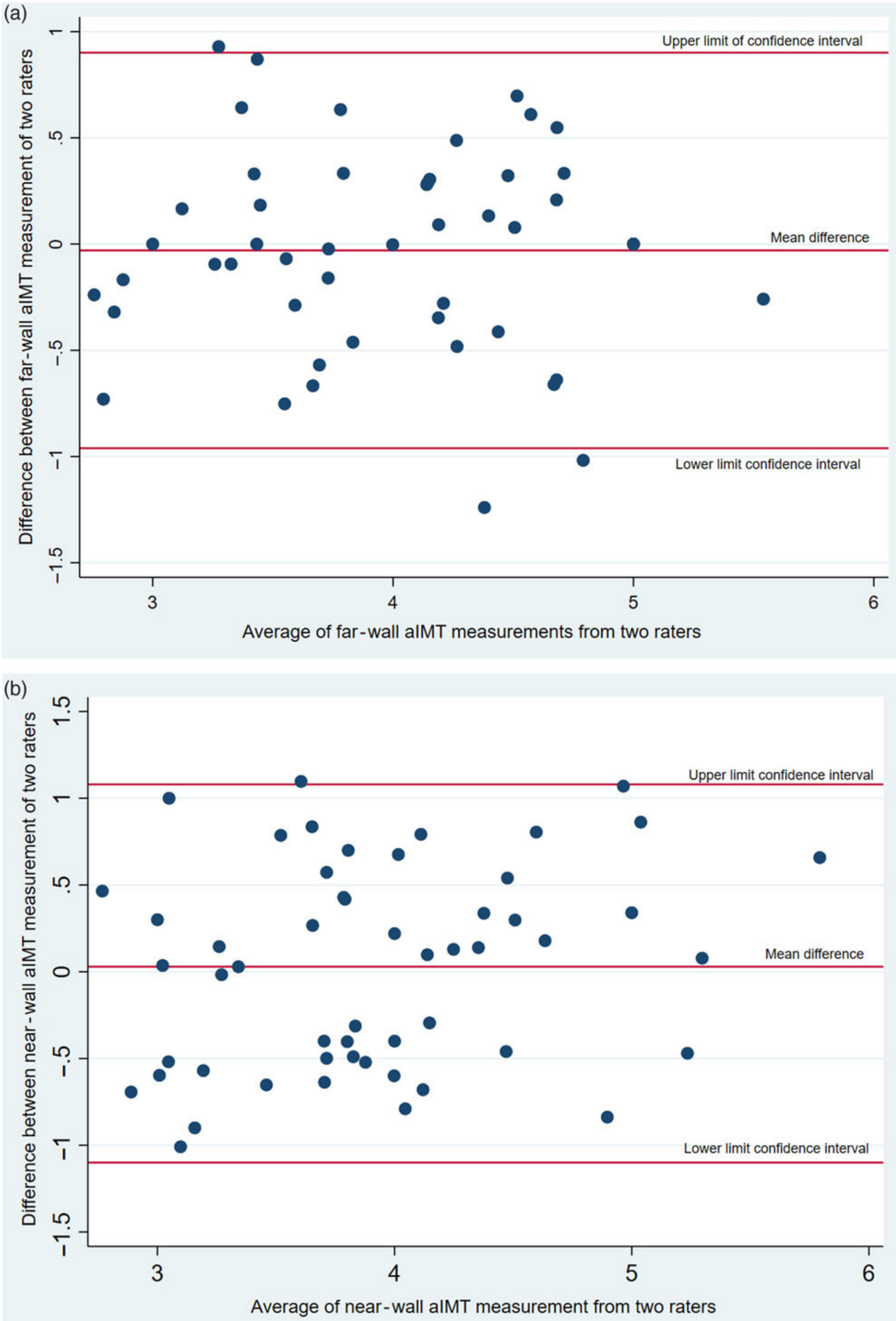

Fig. 1. (a and b). Bland-Altman plot of differences versus mean for inter-rater reliability showing maximum values within 95% confidence intervals for far- and near-wall aortic intima-media thickness (aIMT).

significantly lower amongst mothers of GRF fetuses. Fetal gender, GA at delivery, mode of delivery and admission to nursery or neonatal intensive care unit between the groups showed insignificant differences.

Fetal ultrasound parameters (Table 3 and Figs. 2 and 3)

Compared to AGA fetuses [0.423 mm, IQR: 0.110], median far-wall aIMT was significantly greater in GRF fetuses [0.498 mm, IQR: 0.12] (*P*-value <0.001). Similarly, compared to AGA fetuses [0.398 mm, IQR: 0.110], median near-wall aIMT was significantly greater in GRF group [0.453 mm, IQR: 0.15] (*P*-value < 0.001) (Table 3). Thickness observed in the near wall was significantly less as compared to the far wall, irrespective of fetal growth status (mean difference: 0.023, *P*-value: 0.03). An increasing trend in aIMT in both far- and near-wall measurements was observed as the severity of fetal smallness increased (Fig. 2).

A relative decrease in aD was also observed with increasing severity of growth restriction, however, it did not attain the statistical significance (*P*-value 0.08) (Table 3 and Fig. 3). Umbilical artery PI was found to be increased and cerebral placental ratio decreased significantly in GRF as compared to AGA group. Uterine arteries and middle cerebral artery PI, however, did not show significant difference.

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Table 1. Maternal characteristics by fetal growth status

Variables	AGA ($n = 102$)	GRF ($n = 34$)	*P*-value
Maternal age (years)[a]	31 (6)	31 (9)	0.58
First-trimester BMI[a]	27.7 (9.3)	25.0 (5.4)	0.03
Parity[b]			
Primiparous	56 (54.9)	20 (58.8)	0.69
Multiparous	46 (45.1)	14 (41.2)	
Hyperglycemia in pregnancy[b]	43 (42.1)	7 (20.6)	0.02
Hypertensive disorders of pregnancy[b]	16 (15.7)	3 (8.8)	0.34

AGA, appropriate for gestational age; BMI, body mass index; GRF, growth-restricted fetuses.
[a]Median with interquartile range.
[b]Frequency with percentages.

Table 2. Neonatal characteristics by fetal growth status

Variables	AGA ($n = 102$)	GRF ($n = 34$)	*P*-value
Gender[a]			
Female	48 (47.1)	20 (58.8)	0.23
Male	54 (52.9)	14 (41.2)	
Gestational age at delivery (weeks)[b]	37 (1)	37 (2)	0.05
Birth weight (g)[c]	2866.7 (±446.6)	2087.1 (±288.4)	<0.001
Newborn admission[a]			
Nursery	96 (94.1)	30 (88.2)	0.10
NICU	6 (5.8)	4 (11.8)	

NICU, neonatal intensive care unit.
[a]Frequency with percentages.
[b]Median with interquartile range.
[c]Mean with a standard deviation.

Adjusted model (Table 4)

Multivariable model revealed that GRF had significantly thicker far-wall aIMT (adj. $\beta = 0.082$, 95% CI 0.042–0.123) compared to AGA, when adjusted for maternal age, first-trimester BMI, fetal gender, hypertensive disorders and hyperglycemia in pregnancy. Keeping the same variables constant during adjustment, near-wall aIMT was also found to be significantly thicker for GRF (adj. $\beta = 0.049$, 95% CI 0.010–0.089). However, aD did not attain statistical significance in the adjusted model (adj. $\beta = -0.591$, 95% CI −1.211 to 0.028).

Subgroup analysis (Tables 5 and 6)

Compared to AGA fetuses, significantly thicker far- and near-wall aIMT and significantly smaller aD were observed for IUGR fetuses. In SGA fetuses, only the far wall was significantly thicker. When compared with SGA fetuses, both the far- and near-wall aIMT measurements were significantly greater for IUGR group.

Discussion

Our study demonstrates that vascular programming occurs at a fetal stage in a compromised undernourished intrauterine environment as evaluated through measurement of fetal abdominal aortic wall thickness and diameter. Our aggregated comparison (GRF vs. AGA) indicated influence on all three parameters, that is, far- and near-walls aIMT and aD. Segregated analysis further highlighted that severity of growth restriction (as in IUGR fetuses) further aggravates the vascular insult.

The pathophysiological alteration in the aortic endothelial vessel wall in GRF could be due to a decrease in growth factors like IGF-I following nutritional compromise during the critical prenatal period.[13] Increased far-wall thickness observed in both IUGR and SGA fetuses suggest it to be an area of higher derangement in comparison to near wall. The location just before abdominal aortic bifurcation is often considered as a lesion prone site for endothelial derangement.[10] Detection of vascular changes in far wall amongst SGA fetuses indicates its susceptibility even in the absence of severity markers based on Doppler assessment parameters. On the other hand, the insignificant difference observed in the near-wall thickness of SGA group could be due to their less susceptibility to damage in response to a very mild form of placental insufficiency. Overall, a lesser near-wall ultrasonography measurement as compared to far wall should be interpreted with caution, as gross changes in near-wall thickness are reported to be 20% less evident when compared to its histologic measurements.[24]

Our findings are consistent with far-wall aIMT observations for IUGR fetuses when compared to AGA group by Cosmi *et al.* who observed persistence of these differences when followed during infancy.[14] Gomez *et al.* reported a similar significant difference

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Table 3. Ultrasound parameters by fetal growth status

Variables	AGA ($n = 102$)	GRF ($n = 34$)	P-value
Gestational age at ultrasound (weeks)	36.1 (1.6)	35.9 (1.5)	0.74
Estimated fetal weight (g)	2451 (277)	1958 (510)	<0.001
Z-scores	−0.26 (0.7)	−1.8 (0.71)	
Far-wall aIMT (mm)	0.423 (0.11)	0.498 (0.12)	<0.001
Near-wall aIMT (mm)	0.398 (0.11)	0.453 (0.15)	0.001
Aortic diameter (mm)	4.81 (1.98)	4.65 (1.48)	0.08
Uterine artery PI	0.77 (0.1)	0.81 (0.2)	0.29
Umbilical artery PI	0.85 (0.1)	0.92 (0.2)	0.007
Middle cerebral artery PI	1.78 (0.3)	1.73 (0.4)	0.20
Cerebro-placental ratio	2.06 (0.5)	1.87 (0.7)	<0.001
Biparietal diameter (mm)	89.0 (4.8)	87.3 (6.5)	0.001
Z-score	−0.37 (1.5)	−1.29 (1.2)	<0.001
Occipito-frontal diameter (mm)	109.3 (4.7)	106.2 (7)	<0.001
Z-score	−0.40 (1.0)	−1.07 (0.8)	<0.001
Head circumference (mm)	311.1 (13.3)	301.4 (22.3)	<0.001
Z-score	−0.70 (1.3)	−1.4 (1.3)	<0.001
Abdominal circumference (mm)	303.2 (26.5)	291.1 (28.9)	<0.001
Z-score	−0.35 (1.1)	−1.9 (0.7)	<0.001
Femur length (mm)	67.3 (3.9)	64.7 (3.1)	<0.001
Z-score	0.40 (1.48)	−0.84 (1.0)	<0.001

aIMT, aortic intima-media thickness; PI, pulsatile index.
All values are presented in median with interquartile range.

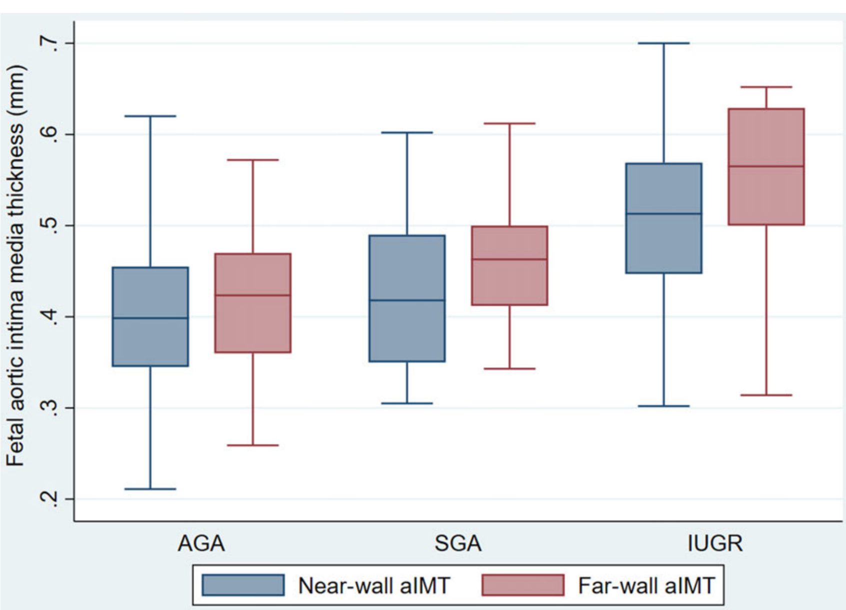

Fig. 2. Near- and far-wall aIMT based on *in-utero* growth status.

in far-wall aortic parameters between IUGR and AGA fetuses as well as between IUGR and SGA fetuses.[15] However, in contrast to our observations, they did not find a significant difference in far-wall aIMT of SGA in comparison to AGA fetuses. In contrast, our study showed an increased far-wall aIMT thickness in the SGA group compared to AGA, indicative of possible endovascular remodelling initiation without evident signs of severe nutritional compromise.[25] Stergiotou *et al.* also demonstrated a thicker far wall in SGA neonates born at term.[26] The magnitude of vascular damage was however worse amongst IUGR fetuses.

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Table 4. Univariate and multivariable model for the association of fetal growth restriction to the far-wall and near-wall abdominal aortic intima-media thickness

Variables		Univariate				Multivariable[b]			
		β-coefficients	95% CI Lower	Upper	*P*-value	β-coefficients	95% CI Lower	Upper	*P*-value
Far wall	GRF[a]	0.090	0.058	0.121	<0.001	0.082	0.042	0.123	<0.001
Near wall	GRF[a]	0.063	0.030	0.095	<0.001	0.049	0.010	0.089	<0.014
Aortic diameter	GRF[a]	−0.525	−0.992	−0.058	0.02	−0.591	−1.211	0.028	0.06

CI, confidence interval.
[a]Reference Category: AGA.
[b]Adjusted for maternal age, booking BMI, fetal gender, hypertensive disorders and hyperglycemia in pregnancy.

Table 5. Subgroup analysis for abdominal aortic intima-media thickness and aortic diameter comparison amongst AGA, SGA, and IUGR fetuses

Groups	Far-wall thickness (mm)	Near-wall thickness (mm)	Aortic diameter (mm)
AGA	0.423 (0.110)	0.398 (0.110)	4.81 (1.98)
SGA	0.463 (0.088)	0.418 (0.140)	4.78 (1.21)
IUGR	0.565 (0.129)	0.513 (0.122)	4.30 (1.49)
P-values for between-group differences			
AGA versus SGA	0.01	0.24	0.43
AGA versus IUGR	<0.001	<0.001	0.05
SGA versus IUGR	0.005	0.04	0.34

AGA, appropriate for gestational age fetuses; IUGR, intrauterine growth restricted; SGA, small for gestational age fetuses.
All values are presented in median with interquartile range.

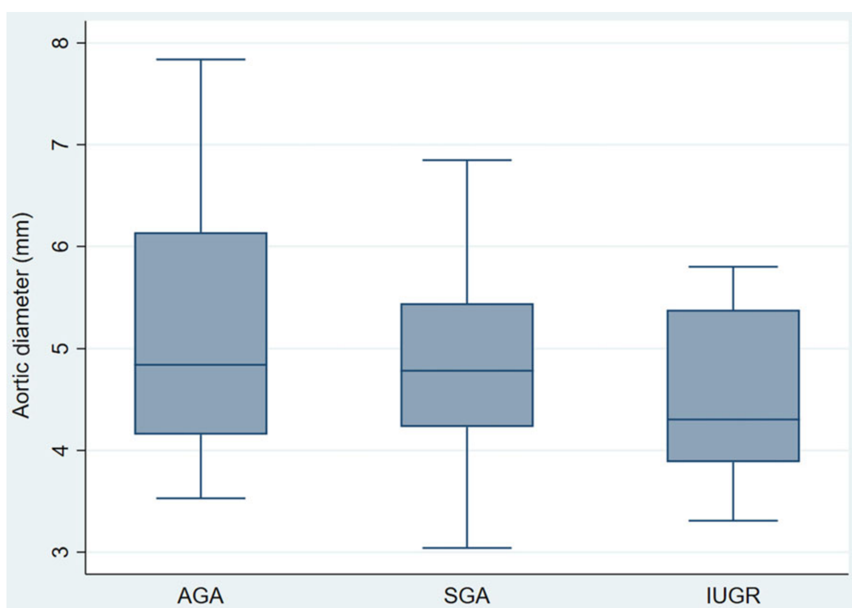

Fig. 3. The difference in aortic diameter based on *in-utero* growth status.

Unlike previous studies,[14,15] we accounted for other clinical covariates of fetal aIMT such as maternal age, first-trimester BMI, fetal gender, hypertensive disorders and hyperglycemia in pregnancy which improved validity of our findings. In addition, to the best of our knowledge, our study is the first to examine the near-wall component of the aortic vascular tree beside far-wall measurements. Applying a stringent criterion for defining fetal smallness further allowed us to examine the vascular remodelling in both SGA and IUGR groups. Finally, the use of a noninvasive ultrasound procedure for measuring aIMT supports its feasibility and reproducibility. However, possibility of nondifferential misclassification of aIMT measurements due to the manual placement of callipers could not be ruled out.

In summary, our study indicates that GRFs demonstrate changes in the aortic wall structure and hence, are potentially susceptible for future cardiovascular disease risk than AGA group.

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Table 6. Univariate and multivariable model for the association of subgroups of fetal growth restriction to the far-wall and near-wall abdominal aortic intima-media thickness and aortic diameter

Variables		Univariate				Multivariable[b]			
		β-coefficients	95% CI Lower	Upper	P-value	β-coefficients	95% CI Lower	Upper	P-value
Far wall	Fetal subgroups[a]								
	SGA	0.053	0.015	0.091	0.006	0.057	0.006	0.107	0.02
	IUGR	0.136	0.093	0.178	<0.001	0.113	0.059	0.167	<0.001
Near wall	Fetal subgroups[a]								
	SGA	0.030	−0.009	0.069	0.134	0.036	−0.013	0.086	0.15
	IUGR	0.104	0.060	0.148	<0.001	0.065	0.011	0.119	0.01
Aortic diameter	Fetal subgroups[a]								
	SGA	−0.450	−1.081	0.179	0.15	−0.456	−1.246	0.333	0.24
	IUGR	−0.759	−1.457	−0.062	0.03	−0.752	−1.603	0.098	0.08

[a]Reference Category: AGA.
[b]Adjusted for maternal age, booking BMI, fetal gender, hypertensive disorders, and hyperglycemia in pregnancy.

Assessment of vascular remodelling at an early stage of life is feasible through simple non-invasive ultrasound markers such as abdominal aorta intima-media thickness and diameter. Early identification *in-utero* through these screening tools would provide a window of opportunity for targeted postnatal intervention such as the promotion of exclusive breastfeeding, increased consumption of fruits and vegetables and increased physical activity so as to reduce the possibility of cardiovascular disease later in life. In addition, it would be desirable that these undernourished neonates are followed during their late childhood and adolescence for their progressive risk monitoring.

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Conflicts of interest. None.

Ethical standards. All steps of the study were in accordance with the institutional guidelines and ethical approvals.

Details of contributors. NM contributed towards the project conceptualisation and design, supervised the project implementation, performed offline data analysis and provided expert advice and critical revisions of several manuscript drafts for important intellectual content.

ZA contributed towards the design and conducted the study, performed offline analysis and prepared the initial drafts and manuscript revisions. RN provided expert advice for study design and data interpretation and critically revised several drafts for important intellectual content. IA contributed towards data analysis and interpretation and critically revised the final draft. AM contributed towards the conduct of the study and critically revised the final draft. All authors contributed and agreed to the final version of the manuscript.

Data availability. Because of organizational agreements, the data supporting this manuscript cannot be made available publicly. The Fetal Medicine Unit can provide the data upon individual requests, subject to appropriate approvals.

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