Fetal Endothelial Remodeling in Late-Onset Gestational Hypertension

Silvia Visentin,[1] Ambrogio Pietro Londero,[2] Beatrice Bellamio,[1] Grazia Giunta,[1] Chiara Cosma,[3] Diego Faggian,[3] Mario Plebani,[3] and Erich Cosmi[1]

BACKGROUND
Recent studies reveal that offspring of pregnancies complicated by hypertensive disorders may have an increased cardiovascular risk. Genetic and nongenetic factors seem to play an important role in premature arterial disease. Endothelium may be significant for long-term remodeling of the arterial wall. The aim of the study was to assess fetal endothelial and renal function in late-onset gestational hypertension.

MATERIALS AND METHODS
This was a case-controlled study. Singleton pregnancies affected by late-onset gestational hypertension (after 34 weeks' gestation) and controls were included. Ultrasound examinations (fetal biometry, fetal Doppler, fetal aorta intima media thickness (aIMT), fetal kidney volumes, maternal Doppler, presence of uterine arteries protodiastolic notching from anomaly scan) and clinical data were collected. A sample of amniotic fluid was taken at delivery.

RESULTS
Fifty patients with late-onset hypertension and 50 controls were included. At growth scan (weeks 29–32) we found in the study group significantly higher fetal aIMT, umbilical artery pulsatility index (PI), fetal aorta PI, and mean uterine arteries PI with persistent bilateral notch. In the case group microalbuminuria levels were significantly higher than controls (1.32 ± 0.11 vs. 1.10 ± 0.13 g/l, $P < 0.0001$), and there was a negative correlation between renal fetal volume at growth scan and amniotic microalbuminuria (r: −0.95, 95% C −0.97 to −0.90, $P < 0.0001$).

CONCLUSIONS
Gestational hypertension should be considered as one of the adverse early risk factors that might predispose to impaired fetal cardiovascular development during intrauterine life; therefore, this study provides further evidence to better understand the origins of cardiovascular diseases.

Keywords: blood pressure; late onset hypertension; renal failure; vascular remodeling.

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Gestational hypertensive disorders (HPDs) during pregnancy complicate about 5–8% of pregnancies, late preterm onset (between 34 and 37 weeks of gestation) represents in 5–17% of these,[1] and they are associated with poor maternal and pregnancy outcomes.[2] A recent systematic review found that fetuses exposed to maternal preeclampsia had higher mean systolic and diastolic blood pressure during childhood and young adulthood, compared with those not exposed to preeclampsia *in utero*.[3] Several risk factors for arterial diseases, such as dyslipidemia, diabetes mellitus, and hypertension, are hereditary. However, predisposition to cardiovascular disease may be influenced by genetic factors acting independently of these risk factors and through pathways of thrombosis, inflammation, and lipid metabolism.[4] Early endothelial dysfunction, chronic inflammation, and impaired arterial vasodilation occurring *in utero* may have an important role in premature *in utero* stiffening of the vessels and might predispose these individuals to hypertension and nephropathies in adulthood.[5] Considering the prevalence of the disease in pregnancy, these findings are potentially relevant to the cardiovascular health of 300 million people worldwide.[6] An association between aortic wall intima media thickening (aIMT) and low birth weight in fetuses or during childhood has already been studied.[7–9] Moreover, developing kidneys appear to be extremely susceptible to low birth weight and several studies have described a reduced number of nephrons after intrauterine growth restriction (IUGR), according to the Brenner's hyperfiltration hypothesis.[10] To monitor the manifestation of kidney and generalized vascular damage, microalbuminuria assessment has been recently recommended in a risk stratification strategy for hypertension management and as a prognostic factor for cardiovascular risk.[11] Nonetheless, the association between maternal gestational HPD and fetal endothelial remodeling mechanisms should be further investigated. A growing body of evidence links pregnancies complicated by HPD to impairment of the offspring's cardiovascular health in childhood and adult life, yet no studies

Correspondence: Erich Cosmi (ecosmi@hotmail.com).

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[1]Department of Woman's and Child's Health, Maternal Fetal Medicine Unit, University of Padua School of Medicine, Padua, Italy; [2]Clinic of Obstetrics and Gynecology, DISM, University of Udine, Udine, Italy; [3]Laboratory Medicine, University of Padua, Padua, Italy.

have been conducted during the intrauterine period.[3] Since it was observed that the offspring of women affected by HPD during pregnancy had an increased risk of developing cardiovascular and kidney diseases,[3,5,12] this led us to hypothesize that fetuses of hypertensive mothers present *in utero* signs of subclinical vascular and renal remodeling.

The aims of this study were (i) to assess fetal vascular function by evaluating fetal aorta, umbilical artery and middle cerebral artery pulsatility index (PI), and abdominal aIMT in fetuses of late hypertensive and normotensive patients; (ii) to evaluate fetal renal function by measuring amniotic fluid albumin concentration and kidney volume in both groups, and (iii) to analyze the maternal blood supply to the placenta by Doppler ultrasound scan in both groups.

MATERIALS AND METHODS

Study population

A case-controlled study was carried out among patients with singleton pregnancies attending their routine anomaly and third trimester hospital scan at a tertiary referral center, the University Hospital of Padua, between January 2013 and June 2014. On a case-by-case basis, we consecutively included singleton pregnancies affected by late gestational hypertension diagnosed after the 34th week of gestation. As controls, we included a one-to-one random sample of normal singleton pregnancies that delivered during the same period. Gestational age was determined from known last menstrual period and ultrasound dating before 20 weeks of gestation. Exclusion criteria were twin pregnancies, major congenital anomalies, pregnancies complicated by maternal history of cardiovascular disease or endocrine disorders such as type I diabetes, gestational diabetes, thyroid and adrenal problems, severe obesity, clinical chorioamnionitis, and preeclampsia. Amniotic fluid samples contaminated with maternal blood were also excluded. Data and samples were prospectively collected. The ethical committee of the Hospital approved the study (P1826, in 2009) and during the first antenatal visit, before commencing, written consent was obtained from the patients. To assess the *in utero* presence of fetal vascular and renal remodeling subclinical signs, we considered the following outcomes: fetal aIMT, abdominal aorta diameter, abdominal aorta PI, umbilical artery PI, middle cerebral artery PI (only starting from the growth scan at 29–32 weeks' gestation), kidney mean volume, microalbuminuria, mean maternal uterine arteries (UtA) PI, mean UtA resistance index, and the presence of notching of the uterine arteries.

Clinical information and instrumental examination

Patients were specifically asked about the method of conception, obstetric, past medical and family history, hypertension in a previous pregnancy and whether they had relatives (up to second degree) with a history of preeclampsia, highest systolic blood pressure or diastolic blood pressure, and use of medication. Demographic (age, ethnicity, parity), lifestyle variables (diet, physical activity, blood pressure, smoking, use of alcohol or drugs), and risk factors for several diseases (obesity, diabetes mellitus, thrombophilia, HPD, preterm delivery, and IUGR) were collected. Pregnancy data during hospitalization and at the time of delivery (development of late hypertension, gestational age at delivery, mode of delivery, neonatal data) were gathered from the hospital maternity records. Patients with gestational hypertension were treated by using methyldopa and nifedipine according to the severity of hypertension and to the response to drug administration. Maternal height and weight were measured and body mass index (BMI) was calculated (kg/m^2).

During every exam we evaluated fetal growth, fetal well-being, and maternal Doppler. Fetal renal volumes were calculated with the following formula: Volume = Length × Width × Thickness × 0.5233, which is the approximation of an ellipsoid.[13] The average volume of the 2 kidneys was used. All the ultrasound scans were performed by 2 skilled operators (S.V. and E.C.) using an ultrasound machine equipped with a 3.5- to 5-MHz linear array transducer (Voluson E8; General Electric Medical Systems, Zipf, Austria). Maternal blood pressure was measured on the left arm following a period of rest of at least 10 minutes; this involved being seated and taking 2 measures at the level of the heart of systolic blood pressure and diastolic blood pressure.[14] The arithmetic mean of the 2 measures was used. Maternal blood pressure was recorded using automated blood pressure devices Myndraj Biomedical Elettronics IMP/9,800. Maternal gestational hypertension was defined as a systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg or more, on at least 2 occasions 4 hours apart, developing after 20 weeks of gestation, with the absence of significant proteinuria.[14] IUGR fetuses were identified according to the fetal weight below the 10th percentile, the fetal abdominal circumference below the 10th percentile, or flattening of the growth curve in the third trimester with umbilical artery Doppler alterations (PI > 2 SD for gestational age) and ultrasonographic signs of placental insufficiency (UtA PI > 2 SD).[15] A sample of amniotic fluid for albumin concentration was obtained before birth by amniocentesis during caesarean section or after spontaneous rupture of membranes during labor. Amniotic fluid albumin was assayed using an immunonephelometric method (BN™II; Siemens Medical Solutions, Malvern, PA).

Fetal aortic intima media thickness and vascular Doppler evaluations

Aortic IMT and diameter were measured as previously described,[8] in a coronal or sagittal view of the fetus, at the dorsal arterial wall of the abdominal aorta, 15 mm below the renal arteries and above the iliac arteries, during anomaly and third trimester scans. Gain settings for aIMT were optimized to obtain the best contrast between the inner blood vessel and the adjacent connective tissue. Abdominal aIMT 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. Three measurements were taken, and the arithmetic mean aIMT was used for the study. Aortic diameter was measured at the same level of aIMT,

from the inner wall to the wall edges. The intraobserver and interobserver agreements were evaluated based on the aIMT measurements obtained by expert practitioners (S.V. and E.C.), blinded among themselves, measuring the aIMT 3 times on the same fetus after a 2-minute waiting period. The procedure was repeated for 30 different fetuses. Images were analyzed offline by automated wall tracking software.[16]

Fetal and maternal vessels were visualized in a longitudinal view. 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 3 consecutive, similar waveforms were obtained. PI and resistance index were measured using the machine software. In particular, with regard to the measurement of UtA PI, a sagittal section of the uterus was obtained, and the cervical canal and internal cervical os were identified. The transducer was gently tilted from side to side and color flow mapping was used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os. Pulsed wave Doppler imaging was used with the sampling gate set at 2 mm to cover the whole vessel and care was taken to ensure that the angle of insonation was <30°. For each side, when 3 similar consecutive waveforms were obtained, the UtA PI was measured, and the lower of the 2 PI values was considered during screening.[16] The presence of a protodiastolic notch in uterine Doppler waveform was also recorded at the anomaly scan. A mean UtA PI >95th percentile as well as bilateral notching were defined as abnormal Doppler velocimetry and they reflect the higher amount of impedance to blood flow distal to the UtA.[17] Bilateral notching was defined as persistent when it continued to present from the anomaly scan until delivery.

Sample size calculation and statistical analysis

The data were analyzed using the R program (version 3.0.1, R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/). The target sample size was at least of 39 subjects per group and 78 subjects in total. According to previous published data, this sample size is sufficient to detect differences in mean aIMT of 0.75 between controls and cases, with power 90%.[8] A 5% significant level and an SD of 1 were assumed. Two-tailed *P*-values <0.05 were considered statistically significant. The aIMT inter- and intra-assessment variability was tested using intraclass correlation coefficient. Normality of variables was assessed using Kolmogorov–Smirnoff test. Comparison between groups was carried out using: Student's *t*-test or Mann–Whitney test for continuous variables, chi-square test or Fisher's exact test for categorical data. Results are presented as mean ± SD, percentage, and absolute numbers. A univariate and multivariate logistic regression analysis was also performed. A value of aIMT higher than the median value of the distribution was considered as the dependent variable, and the study group was considered as independent variable and possible clinical confounding factors available at the time of the ultrasound scan in univariate analysis presented a *P*-value <0.200. Furthermore, the Pearson correlation coefficient was used to assess the presence of any correlation between fetal renal volume and amniotic microalbuminuria.

RESULTS

A total of 50 women affected by late gestational hypertension and 50 women with normal pregnancy satisfying the inclusion criteria were randomly selected. Baseline characteristics of the subjects are shown in Table 1. Women affected by gestational hypertension were more often older, nulliparous, and had higher systolic and diastolic blood pressures, lower gestational age at delivery, and Apgar score at 5 minutes. There were no differences in ethnicity, prepregnancy BMI, lifestyle variables, use of assisted conception techniques, familial history of hypertension, and other risk factors for HPD between the 2 groups. Median methyldopa dose was 0.500 g/day (interquartile range 0.500–0.875) while median nifedipine dose was 30 mg/day (interquartile range 0–60). There were no IUGR fetuses in the study group. Operative and induced deliveries were higher in the study group, with the same prevalence of caesarean section. Table 2 shows the characteristics of the anomaly scan (19–24 weeks' gestation). During this gestational range no significant differences were found in maternal and fetal Doppler values, fetal aIMT, and kidney volumes between the 2 groups. During the growth scan (29–32 weeks' gestation) we found that the study group had significantly higher aIMT, umbilical artery PI, mean UtA PI or resistance index, and persistent bilateral notch (Table 2). In univariate logistic regression analysis, aIMT was significantly increased in fetuses of women affected by late gestational hypertension (odds ratio (OR) 3.143, 95% confidence interval (CI) 1.199–8.241, and $P < 0.05$), and this finding was still significant after multivariate adjustment for maternal age, parity, and BMI (OR 3.673, 95% CI 1.186–11.372, and $P < 0.05$). Intraobserver and interobserver interclass correlation coefficient of aIMT measurement were 0.876 and 0.856, respectively. We also analyzed data from the late ultrasound scans performed just before delivery during the course of 36th gestational week (34–37 weeks) (Table 2), finding the same results as 29–32 weeks, except for statistically lower kidney volumes (13,622.71 ± 2,656.38 in study group vs. 16,943.5 ± 5,648.78 in controls, $P < 0.05$). Finally, we analyzed the amniotic fluid of both groups. Mean amniotic albumin concentration was significantly higher in the study group than in the control group (1.32 ± 0.11 vs. 1.10 ± 0.13 g/l, $P < 0.0001$) (Figure 1). In univariate logistic regression analysis amniotic albumin concentration was significantly higher in fetuses of women affected by late gestational hypertension (OR 110.222, 95% CI 20.649–588.351, and $P < 0.05$), and this finding was still significant after multivariate adjustment for maternal age, parity, and BMI (OR 203.33, 95% CI 15.561–2656.874, and $P < 0.05$). There was a negative correlation between mean renal fetal volume at growth scan and microalbuminuria levels in amniotic fluid of hypertensive patients (r: −0.95, 95% CI −0.97 to −0.90, $P < 0.0001$) (Figure 2).

DISCUSSION

This study, performed to our knowledge for the first time in fetuses of mothers with late gestational hypertension, showed that they presented with increased aIMT at growth scan (29–32 weeks of gestation), significantly reduced fetal

Table 1. Population description and pregnancy outcomes

	Cases	Controls	*P*
N	50	50	
Women age (years)	34.6 (±7.39)	31.39 (±5.95)	<0.05
Pre-pregnancy BMI (kg/m^2)	26.43 (±4.23)	25.13 (±3.97)	0.160
Nulliparous	52.5%	30%	<0.05
SBP (mm Hg)[a]	150 (±10)	110 (±15)	<0.05
DBP (mm Hg)[a]	100 (±10)	70 (±15)	<0.05
Proteinuria (mg/24 h)[a]	0.20 (±4)	0.10 (±5)	0.230
Mode of delivery			
Spontaneous delivery	25%	40.5%	0.490
Induced delivery	10%	2.5%	0.320
Operative delivery	7.5%	0%	0.070
Caesarean section	57.5%	57.5%	1.000
Gestational age at delivery (weeks)	36.98 (±1.41)	39.27 (±1.5)	<0.05
Neonatal weight (g)	3079.83 (±647.37)	3297.5 (±427.77)	0.120
Percentile of neonatal weight	53.15 (±37.11)	61.27 (±25.82)	0.260
Apgar score at 1st minute	8.89 (±0.68)	9.03 (±0.31)	0.410
Apgar score at 5th minute	9.65 (±0.58)	9.9 (±0.31)	<0.05
Microalbuminuria (g/l)	1.32 (±0.11)	1.10 (±0.13)	<0.05

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]The last measure before delivery.

kidney volumes and higher amniotic microalbuminuria levels in the late third trimester. Women who develop preeclampsia have an increased risk of later developing cardiovascular disease and it has now emerged that there may be cardiovascular health implications for their offspring.[3] Authors of a long-term follow-up study, in fact, found that these offspring had almost double the risk of cardiovascular events in adulthood.[3,18] In this study we found that even fetuses of mother with late gestational hypertension present *in utero* signs of vascular and renal subclinical remodeling. Ultrasound-based measurement of aIMT in fetuses with growth restriction and Doppler abnormalities seems to represent a greater risk of *in utero* preclinical endothelial remodeling and glomerulosclerosis,[8,19,20] hypertension in young children and atherosclerosis in adult life.[21] The supporting data include clinical studies that demonstrate cardiovascular structural and functional changes in children with hypertension.[22,23] Autopsy studies have also confirmed an association of blood pressure with atherosclerotic changes in the aorta as well as heart in children and young adults.[24] Three main mechanisms could explain the associations of maternal hypertension diseases with offspring blood pressure and potentially other measures of cardiometabolic health (familial nongenetic factors, intrauterine environment, and genetic factors). First, a shared familial nongenetic risk factor may be involved such as similar BMI and smoking.[25] Second, a direct intrauterine effect is possible.[25] According to this second mechanism, exposure to maternal hypertension has a lasting effect on cardiac and vascular structure and function, in line with the Barker's hypothesis.[5] There is evidence that late-onset hypertension is a consequence of underlying maternal vascular disease and placental insufficiency; it has been suggested that the latter systemic disease results in, as yet, undetermined vasculotoxic factors released into the maternal circulation with adverse influences on fetal vascular endothelium.[26,27] Alternatively, epigenetic modifications, which might modulate adult phenotype and suggest the induction of permanent genomic marks, might make the fetus highly sensitive to inflammation and oxidative stress, modifying the vascular response to stress.[28–31] Third, blood pressure programming may occur in response to unique biological features of hypertensive diseases and reflect shared genetic factors relevant to both hypertensive diseases and blood pressure control.[28] In fact, genetic variants might account for both higher maternal and offspring blood pressure. Hypertensive diseases are conditions with a heritability of approximately 55%, which is contributed to by both maternal and fetal genes.[32] As pressure diseases result from alterations in multiple atherogenic pathways, multiple loci are probably involved and candidate genes may express themselves only through interaction with other genes or with at-risk lifestyles.[4,33]

Vascular function in neonates or children of hypertensive mothers has been evaluated until now by carotid-femoral pulse wave velocity, brachial flow-mediated dilatation, or carotid intima media thickness. In this study, we evaluated the *in utero* endothelial remodeling in HPD by measuring aIMT, a feasible, accurate, and sensitive marker of atherosclerosis risk, already used in IUGR fetuses, neonates and children.[7,21] The higher aIMT found in case fetuses could be explained by

Table 2. Ultrasound characteristics at morphologic scan (19–24 weeks' gestation), third trimester growth scan (29–32 weeks' gestation), and at last scan (34–37 weeks' gestation)

	19–24			29–32			34–37		
Weeks' gestation	**Cases**	**Controls**	***P***	**Cases**	**Controls**	***P***	**Cases**	**Controls**	***P***
N	50	50		50	50		50	50	
Gestational age at anomaly scan (weeks)	22.93 (±3.00)	23.59 (±2.59)	0.650	30.96 (±1.79)	31.24 (±1.50)	0.489	35.56 (±1.31)	35.64 (±1.36)	0.839
Estimated fetal weight (g)	636.88 (±297.81)	636.25 (±191.12)	0.990	1773.37 (±549.68)	1787.12 (±321.97)	0.908	2554.27 (±487)	2680.05 (±362.22)	0.412
Kidneys mean volume (mm^3)	3826.62 (±1998.99)	3683.46 (±1834.12)	0.890	8394.11 (±3163.31)	9286.41 (±2836.04)	0.231	13622.71 (±2656.38)	16943.5 (±5648.78)	<0.05
aIMT (mm)	0.41 (±0.16)	0.48 (±0.19)	0.490	0.70 (±0.16)	0.55 (±0.2)	<0.05	0.72 (±0.21)	0.61 (±0.17)	0.008
Aorta diameter (mm)	2.91 (±0.76)	2.52 (±0.51)	0.250	3.56 (±0.86)	3.73 (±0.75)	0.375	4.45 (±1.12)	4.08 (±1.31)	0.348
PI of fetal abdominal aorta	1.46 (±0.4)	0.92 (±0.18)	0.271	1.75 (±0.3)	1.37 (±0.25)	<0.05	1.62 (±0.43)	1.48 (±0.33)	0.578
PI of fetal umbilical artery	1.12 (±0.15)	0.92 (±0.21)	0.370	1.1 (±0.27)	0.93 (±0.15)	<0.05	0.91 (±0.09)	0.89 (±0.14)	0.590
PI of fetal median cerebral artery				0.96 (±0.46)	0.79 (±0.31)	0.058	0.83 (±0.28)	0.66 (±0.22)	0.077
Mean PI of maternal uterine arteries	0.96 (±0.54)	0.75 (±0.19)	0.480	1.96 (±0.37)	2.16 (±0.32)	0.218	1.68 (±0.73)	1.93 (±0.25)	0.447
Mean RI of maternal uterine arteries	0.49 (±0.13)	0.48 (±0.13)	0.850	0.6 (±0.33)	0.48 (±0.12)	0.063	0.51 (±0.1)	0.42 (±0.09)	<0.05
Presence of bilateral notch in uterine arteries	14%	0%	<0.05	22%	2%	<0.05	12%	0%	<0.05

Abbreviations: aIMT, aorta intima media thickness; PI, pulsatility index; RI, resistance index.

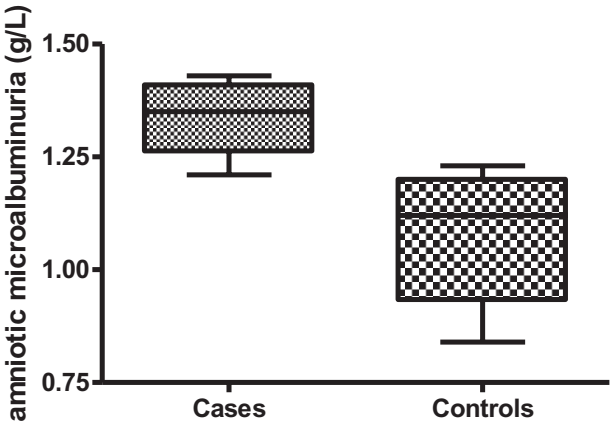

Figure 1. Mean amniotic microalbuminuria levels (g/l) between cases and controls ($P < 0.0001$).

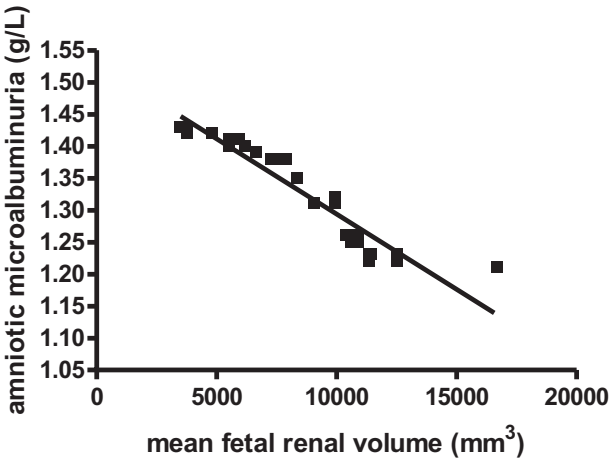

Figure 2. Correlation between mean fetal renal volume and mean amniotic microalbuminuria levels in cases ($P < 0.0001$).

the altered vascular maternal status and the progressive placental insufficiency. A higher mean PI and a persistent bilateral notch of UtA, already present at second trimester scan, were indicative of placental dysfunction,[34] confirming the data present in literature about the predictive role of UtA and bilateral notch as a screening tool for the later development of preeclampsia, IUGR, placental abruption, and stillbirth.[32] Animal models have demonstrated that mild and moderate maternal hypertension were associated with decreasing placental blood flow by 51% and an increase of fetal-to-placental weight ratio, able to differentially alter placental structure and placental gene expression of the renin-angiotensin system without affecting fetal growth, but altering renal development in young offspring.[35,36] These considerations could explain the fact that neonatal birth weight in the study group was not different from that of the controls, and that the higher fetal aorta and umbilical artery PI might be an expression of increased placental resistance, which manifests itself after the 34th week. The subsequent higher intra-aorta pressure could explain the greater fetal aIMT found in case fetuses. Moreover, at 34–37 weeks we found lower fetal renal volume, a possible indirect sign of fetal flow redistribution, and higher amniotic microalbuminuria levels in case fetuses. Singleton and twin IUGR models showed higher albumin creatinine ratio levels in amniotic fluid, possible markers of early glomerulosclerosis.[20] Microalbuminuria is often observed during the early stages of kidney disease due to altered glomeruli permeability of the kidney to protein.[35] Developing kidneys appears to be extremely susceptible to an adverse environment and several studies showed a correlation between the severity of low birth weight, renal size, lower glomerular filtration rates, higher microalbumin secretion, and higher risk of developing several cardiovascular diseases, including hypertension in young adults.[37–39]

The main limitation of the present study is the small sample size, but uniformity of management and previously unpublished results are its major strengths.

In conclusion, the exact underlying link between hypertensive pregnancy disorders and future maternal and fetal cardiovascular disease remains unclear. Exposure to hypertension diseases *in utero* could set offspring on a trajectory for higher blood pressure and renal damage throughout life without investigating cardiometabolic health measures.[40] Whether fetuses of hypertensive pregnancy have a vascular phenotype distinct from other pregnancy complications is not known but, if defined, might give insight into the underlying mechanism for their predisposition to hypertension. It is also unknown whether screening for amniotic albuminuria and aIMT could help to prevent renal function failure, atherosclerosis, and metabolic syndrome at an early stage. These data might represent another step forward in understanding fetal programming in the presence of gestational maternal diseases. Better understanding of the long-term changes in vascular pathophysiology related to different pregnancy complications may allow novel primary cardiovascular prevention strategies targeted at key aspects of vascular function.

DISCLOSURE

The authors declared no conflict of interest.

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