

Cardiovascular Risk Factors in Healthy Women with Previous Gestational Hypertension

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Context: Epidemiological studies indicate that gestational hypertension (Gh) during pregnancy is associated with increased risk of cardiovascular disease in later life. However, it is unclear whether particular metabolic and hemodynamic characteristics are related to this risk.

Objective: The objective of this study was to investigate endothelial function and carbohydrate and lipid metabolism in healthy, normotensive women with previous pregnancy complicated by Gh.

Design, Setting, and Participants: Brachial artery flow-mediated dilatation (FMD; endothelium dependent) and nitroglycerin-induced dilatation (endothelium independent) were measured in 15 subjects with previous Gh and in 15 controls with previous normal pregnancies. Lipid panel, glucose, insulin, homocysteine, and androgens were also measured.

Results: FMD was significantly reduced in women with previous Gh

compared with controls ($P < 0.0001$), whereas nitroglycerin-induced dilatation was comparable in both groups. Gh women showed increased fasting insulin ($P = 0.011$), insulin resistance measured by homeostasis model assessment ($P = 0.018$), free fatty acids ($P = 0.0018$), and testosterone ($P = 0.0012$) and decreased high-density lipoprotein cholesterol ($P = 0.0017$) compared with controls. Across all subjects, FMD showed a strong independent negative correlation with testosterone and homeostasis model assessment and a positive correlation with high-density lipoprotein cholesterol ($r = -0.60$, $P = 0.0003$; $r = -0.43$, $P = 0.016$; and $r = 0.58$, $P = 0.0005$, respectively).

Conclusions: Endothelial dysfunction and early alteration of carbohydrate and lipid metabolism are present in otherwise healthy women with previous Gh. These abnormalities along with a relative hyperandrogenism could explain, at least in part, the increased risk for cardiovascular disease in later life in these women. (*J Clin Endocrinol Metab* 91: 1233–1238, 2006)

GESTATIONAL HYPERTENSION (Gh), namely, the presence of *de novo* blood hypertension after the 20th wk of pregnancy without proteinuria, is a relatively common complication of pregnancy, affecting 2–5% of women. The exact pathophysiology of this disease is still unclear. Recently, studies have demonstrated that Gh is associated with a cluster of metabolic abnormalities, such as hyperinsulinemia, insulin resistance, and dyslipidemia, thus suggesting analogies with the insulin-resistant syndrome (1, 2). According to epidemiological evidence, women with previous Gh seem to be at increased risk for cardiovascular diseases. Jonsdottir *et al.* (3) in a population of 7543 women found that those with hypertension during pregnancy had an augmented risk of death for heart ischemia in later life compared with the general population, with a significantly higher relative risk among eclamptic women and those with preeclampsia than in those with hypertension alone. More recently, Wilson *et al.* (4) reported an increased risk of hypertension and stroke in women with a history of Gh, similar to that observed in women with previous preeclampsia.

Reduced insulin sensitivity, altered angiogenesis and endothelial function, and relative hyperandrogenemia found in

women with previous preeclampsia have been indicated to contribute to their increased risk of cardiovascular disease (5–7). We hypothesize that similar abnormalities may have a role on the increased cardiovascular risk of women with previous Gh. To test this hypothesis, we investigated whether healthy, normotensive women with previous pregnancy complicated by Gh have carbohydrate and lipid metabolic derangement typical of the insulin-resistant state. Furthermore, given that endothelial dysfunction represents an early indicator of cardiovascular risk (8–10), we performed an *in vivo* evaluation of endothelial function in these women.

Subjects and Methods

This study was conducted at Catholic University (Rome, Italy) and was approved by the institutional review board. Informed consent was obtained from each subject before the study. During the study, approximately 1000 women were seen at our outpatient care center for routine gynecological clinical examination. Of these, 36 had a previous pregnancy complicated by Gh, defined as diastolic blood pressure of 90 mm Hg or more at two consecutive measurements 6 h apart with the patient resting in the semirecumbent position, without proteinuria greater than 0.3 g/24 h or more than 1 g/liter (or 2+ with dipstick) in a random sample. According to the International Society for the Study of Hypertension in Pregnancy criteria, the elevation in blood pressure was diagnosed after 20 wk gestation in a previously normotensive woman (11).

In all cases, more than 12 months had elapsed since the delivery (20.4 ± 1.5 months). Those who during the pregnancy had the coexistence of gestational diabetes were excluded, as were those who smoked; drank more than 60 g alcohol/d; were clinically diagnosed with liver disease, hypertension, diabetes, renal disease, or were taking birth control pill; or medications known to affect endothelial function or glycemic and lipid metabolism. Twenty-four women who met the above conditions were approached to participate in the study. Fifteen agreed to be

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Abbreviations: FFA, Free fatty acid; FMD, flow-mediated dilatation; Gh, gestational hypertension; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein.

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enrolled. Twenty-two nonsmoking, healthy women with previous normal pregnancy were approached to participate in the study as controls. All were matched with the study group patients for age and body mass index [calculated as the ratio between weight (in kilograms) and height (in meters) squared]. Fifteen agreed to be enrolled.

All women, those with and without Gh, were followed for the entire length of their previous pregnancies in our department, and all data regarding family history of hypertension, diagnosis of hypertension, birth weight, birth weight percentile, and week of delivery were obtained by our chart record. Subjects in both groups had regular menses every 27–31 d and no clinical signs of hyperandrogenism.

The studies were carried out over 2 d. On d 1, glucose, insulin, homocysteine, androgens, and lipid measurements were made. On d 2, bioelectrical impedance, blood pressure, and endothelial function were measured. The investigations were performed in the morning after abstaining from alcohol, caffeine, and food for 8 h, in a supine position at a temperature of about 25°C. Given that previous studies have shown that endothelial function may vary according to the phase of menstrual cycle, with a substantial impairment during the luteal phase, all subjects were studied during the midfollicular phase (12).

Measurement of endothelial function

The ultrasound investigation for measuring endothelium-dependent and -independent arterial dilatation was performed as described previously (13). Briefly, brachial artery diameter was measured by B-mode ultrasound image using a 7.5-MHz linear array transducer and a standard ESAOTE AU 570 A system (Ansaldo, Milan, Italy). In all studies, scans were obtained with the subject at rest, during reactive hyperemia, again with the subject at rest, and after sublingual administration of nitroglycerin. The velocity of arterial flow was measured with a pulsed Doppler signal. Increased flow was induced by the inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mm Hg for 4.5 min, followed by release. A scan was performed continuously for 30 sec before and 90 sec after deflation of the cuff, including a repeat recording of flow velocity for the first 15 sec after the cuff was released. Thereafter, 10–15 min was allowed for recovery of the vessel, after which an additional resting scan was performed. A sublingual nitroglycerin spray (400 µg) was then administered, and 3–4 min later, the last scan was performed. For the reactive hyperemia scan, measurements of diameter were taken 50–60 sec after deflation of the cuff. The vessel diameter in scans obtained after reactive hyperemia [flow-mediated dilatation (FMD)] and the administration of nitroglycerin (nitrate-induced dilatation) was expressed as a percentage of the average diameter of the artery in the two resting (or control) scans (considered 100%). Reactive hyperemia was calculated as the maximal flow recorded in the first 15 sec after cuff deflation divided by the flow during the first resting (baseline) scan.

Analytical methods

Plasma glucose levels were measured by the glucose oxidase method (Beckman, Fullerton, CA), and all hormone levels were determined using commercial RIA kits (Radim, Rome, Italy). Insulin resistance was calculated by homeostasis model assessment [HOMA; fasting plasma insulin (microunits per milliliter) × fasting plasma glucose (millimoles per liter)/22.5]. The free testosterone index was calculated as previously reported (14).

Total cholesterol and triglyceride concentrations were determined by an enzymatic assay (Bristol, Paris, France). High-density lipoprotein (HDL) cholesterol was determined after precipitation with polyethylene glycol 6000 (Delchimica Scientific, Naples, Italy). Low-density lipoprotein (LDL) cholesterol was isolated by sequential flotation in a Beckman model L7–65 ultracentrifuge using a type 70 rotor (Beckman). Free fatty acids (FFAs) were determined using an acyl-coenzyme A oxidase-based colorimetric method. Total plasma concentrations of homocysteine were estimated by HPLC.

Body composition

Bioelectrical impedance to estimate the subject's body composition was performed with a tetrapolar impedance plethysmograph (Soft Tis-

sue Analyzer, Akern Bioresearch, Florence, Italy) according to Lukaski et al. (15). Briefly, at 0700 h, each woman lay supine on a bed made of nonconductive materials. Detecting electrodes (Red Dot, 3M Health Care, St. Paul, MN) were placed in the middle of the dorsum of hands and feet proximal to the metacarpal-phalangeal metatarso-phalangeal joints, respectively, and also medially between the distal prominences of the radius and the ulna and between the medial and lateral malleoli at the ankle. The current-introducing electrodes were placed at a minimum distance of the diameter of the wrist or ankle beyond the paired detector electrode. An excitation current of 800 mA alternating current at 50 kHz was introduced at the distal electrodes, and the voltage drop across the patient was detected by the proximal electrodes. The percentage of body fat, fat-free mass, and total body water were calculated using the appropriate software (Bodygram, Akern Bioresearch, Florence, Italy).

Statistical analysis

Comparison between groups was performed using Student's unpaired *t* test. Comparisons between frequencies were assessed by χ^2 analysis. Linear regression analysis was used for relationships between FMD and the metabolic characteristics studied. Subsequently, variables whose correlation with FMD achieved near-statistical significance ($P \leq 0.1$) were entered into a stepwise regression model to assess the magnitude of their individual effects on FMD. The sample size for FMD was calculated for a power of 0.80, assuming a difference in means of approximately 5 and an SD of approximately 3 from our previous findings (16). Data are given as the mean \pm SD. Statistical significance was accepted at a level of $P < 0.05$.

Results

Demographic and pregnancy characteristics of the control and the previous Gh group are shown in Table 1. There were no significant differences with regard to age, body mass index, percentage of fat mass, and waist/hip ratio. By design, systolic and diastolic blood pressures during the previous pregnancy were higher in women with previous Gh. The glucose area during the oral glucose tolerance test was slightly, but not significantly, higher in women with Gh.

Metabolic characteristics

Fasting insulin levels and HOMA were 60% and 80% higher in women with previous Gh than in control subjects ($P = 0.006$ and $P = 0.005$, respectively; Table 2). Both groups had similar fasting glucose levels. All subjects had normal lipid profiles; however, women with previous Gh exhibited more than 20% lower HDL and roughly 60% higher FFA than controls ($P = 0.0017$, and $P = 0.0018$, respectively; Table 2). Triglycerides, total cholesterol, and LDL cholesterol were comparable in the two groups.

All subjects showed androgen levels in the normal range; nevertheless, women with previous Gh had higher total and free testosterone levels than control subjects ($P = 0.0012$ and $P = 0.0025$, respectively, Table 2). SHBG concentrations were somewhat lower in the group with previous Gh compared with controls, but the difference between groups did not reach statistical significance.

Hemodynamic data

Although all subjects were normotensive, both systolic and diastolic blood pressures were significantly higher in women with previous Gh (Table 2). Baseline brachial artery diameter (vessel size) was similar in the two groups (Table 2). Baseline velocity and the percent increase in blood ve-

TABLE 1. Demographic and pregnancy characteristics

	Controls (n = 15)	Previous Gh (n = 15)	P value	Power %
Data at study				
Age (yr)	37.6 ± 1.5	34.3 ± 1.2	0.14	33
BMI (kg/m ²)	23.5 ± 0.8	24.4 ± 1.3	0.29	23
FM (%)	27.0 ± 1.4	28.4 ± 2.4	0.63	7
Waist/hip ratio	0.82 ± 0.006	0.83 ± 0.005	0.27	19
Index pregnancy data				
Parity (1/ >1 pregnancies)	11/4	14/1	0.14	
Family history of hypertension	5/10	8/7	0.45	
SBP (mm Hg) ^a	106.0 ± 3.6	140.3 ± 1.3	<0.0001	
DBP (mm Hg) ^a	68.7 ± 1.3	93.0 ± 1.1	<0.0001	
AUC glucose ^b	14,955 ± 518	15,691 ± 571	0.36	23
Birth weight (g)	3,221 ± 118	2,867 ± 235	0.19	23
Birth weight percentile	52.5 ± 8.3	46.8 ± 7.5	0.61	7
Gestation at delivery (wk)	39.2 ± 0.4	37.9 ± 1.0	0.28	17

BMI, Body mass index; FM, fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; Power %, percent probability of correctly detecting a significant difference.

^a Highest values without antihypertensive therapy during pregnancy.

^b AUC expressed as mg/dl × 180 min, available in nine controls and 12 previous Gh women. Values are expressed as mean ± SEM.

locity after ischemic stimulus (reactive hyperemia) were comparable in the groups. FMD (*i.e.* endothelium-dependent dilatation) of previous Gh women was nearly 55% that of controls ($P < 0.0001$). Nitroglycerin-dependent dilatation (endothelium-independent dilatation) was comparable in the two groups.

Correlational analyses

To better investigate the relation between endothelial function, carbohydrate and lipid metabolism, and hormone status, we performed linear regression analysis between FMD and the various parameters examined. Linear regression analysis showed that total testosterone levels had a strong negative association with FMD ($r = -0.600$; $P = 0.0003$). A similar, if less robust, correlation was found between FMD and free testosterone ($r = -0.57$; $P = 0.0007$; Fig.

1A). Negative significant correlations were also found between FMD and HOMA as well as between FMD and fasting insulin ($r = -0.43$; $P = 0.0163$ and $r = -0.41$; $P = 0.024$; Fig. 1, B and C, respectively). Conversely, FMD exhibited positive relations with HDL cholesterol ($r = 0.58$; $P = 0.005$; Fig. 1D). A significant correlation was also found between FMD and body mass index ($r = -0.36$; $P = 0.046$).

Androgens, hyperinsulinemia/insulin resistance, adiposity, and lipids all may affect endothelial function. Therefore, to evaluate their independent contributions to prediction of FMD, we performed stepwise regression analysis. The analysis revealed that total testosterone accounted for 34% of the variance in FMD ($P = 0.0005$), whereas HOMA and HDL cholesterol contributed an additional 22% and 3%, respectively ($P < 0.0001$ in both cases; Table 3). The other variables analyzed did not contribute to the regression model.

TABLE 2. Comparison of metabolic and vascular characteristics between controls and women with previous Gh

	Controls (n = 15)	Previous Gh (n = 15)	P value	Power %
Fasting glucose (mg/dl)	83.3 ± 1.8	89.1 ± 2.6	0.08	38
Fasting insulin (μU/ml)	5.5 ± 0.6	8.8 ± 0.9	0.006	
HOMA	1.13 ± 0.12	2.0 ± 0.24	0.005	
Homocysteine (μmol/liter)	7.7 ± 0.4	8.2 ± 0.8	0.54	8
Triglyceride (mg/dl)	78.3 ± 10.5	83.5 ± 7.0	0.68	6
Uric acid (mg/dl)	3.7 ± 0.3	4.5 ± 0.2	0.017	
Total cholesterol (mg/dl)	177.9 ± 13.2	182.9 ± 6.4	0.73	5
HDL-cholesterol (mg/dl)	64.9 ± 3.3	51.3 ± 2.1	0.0017	
LDL-cholesterol (mg/dl)	111.4 ± 4.9	114.3 ± 6.1	0.71	5
FFA (mg/dl)	0.25 ± 0.06	0.71 ± 0.04	0.0018	
Testosterone (ng/ml)	0.26 ± 0.03	0.46 ± 0.04	0.0012	
SHBG (nmol/liter)	84.4 ± 8.4	63.9 ± 11.4	0.159	26
Free testosterone (pg/ml)	0.39 ± 0.07	1.02 ± 0.17	0.0025	
SBP (mm Hg)	115.3 ± 3.3	126.6 ± 2.9	0.015	
DBP (mm Hg)	69.3 ± 2.0	77.0 ± 1.5	0.006	
Vessel size (mm)	2.8 ± 0.07	3.0 ± 0.15	0.185	23
FMD (%)	19.8 ± 1.3	8.9 ± 1.1	<0.0001	
NID (%)	28.1 ± 2.7	27.7 ± 1.7	0.88	4
Baseline velocity (m/sec)	0.11 ± 0.03	0.06 ± 0.01	0.076	39
Reactive hyperemia (%)	331 ± 89	427 ± 45	0.34	14

SBP, Systolic blood pressure; DBP, diastolic blood pressure; NID, nitrate-induced vasodilatation. Values are expressed as mean ± SEM. Power %, Percent probability of correctly detecting a significant difference. Conversion factors to SI units: glucose × 0.0551 (mmol/liter); insulin × 7.175 (pmol/liter); triglyceride × 0.0113 (mmol/liter); uric acid × 59.48 (μmol/liter); total cholesterol, HDL, and LDL × 0.0259 (mmol/liter); FFA × 0.03906 (μmol/liter); T and free T × 3.467 (nmol/liter).

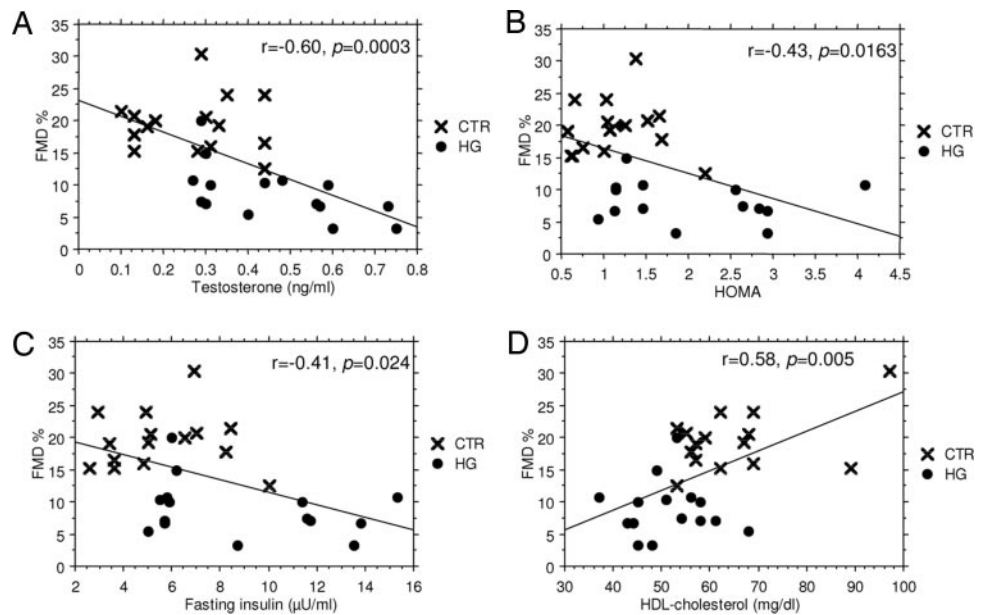


FIG. 1. Linear regression analysis between percent increase in FMD and testosterone (A), HOMA (B), fasting insulin (C), and HDL cholesterol (D).

Discussion

The results of this study reveal the following new findings. 1) Seemingly healthy women with a history of previous Gh show impaired FMD compared with controls. 2) FMD is strongly and negatively related to testosterone levels. 3) Early derangement of carbohydrate and lipid metabolism is present in these subjects.

FMD was examined, under resting conditions, by measuring the percent increase in vessel diameter in response to increased blood flow during postocclusion hyperemia. It is recognized that FMD depends on the ability of the endothelium to release nitric oxide in response to shear stress and is used as a reliable method to assess endothelial function in various clinical conditions (17). Although, to our knowledge, no previous studies have assessed endothelial function in women with previous Gh, our results are consistent with reports that women with a history of preeclampsia have endothelial dysfunction (6, 18). Chambers *et al.* (6) in a case-control study analyzed brachial artery FMD in 113 women with previous preeclampsia and in 48 women with previous uncomplicated pregnancies. They found that women with previous preeclampsia had a significant lower FMD than controls ($P < 0.001$), concluding that these women had impaired endothelial function (6). More recently, similar findings were reported by Agatista *et al.* (18), leading the researchers to deduce that women with history of preeclampsia are at increased risk for cardiovascular disease. Some re-

searchers believe that gestational, nonproteinuric hypertension is a mild variety of preeclampsia (19). If this assertion is true with regard to the pregnancy's prognosis, it cannot be extended to postpregnancy life, when, as shown by our results, women with previous Gh have alteration of endothelial function as do women with previous preeclampsia.

As stated in *Subjects and Methods*, all subjects studied were normotensive. Despite that, women with a history of Gh presented 10% higher systolic and diastolic blood pressures compared with controls. It is known that hypertension is associated with endothelial dysfunction (20). Thus, one could hypothesize that this difference in blood pressure may account for the blunted endothelial function observed in previous Gh patients. However, as previously demonstrated in healthy and obese subjects (21), we did not find a significant correlation across all subjects among FMD, systolic blood pressure, and diastolic blood pressure ($r = -0.25$; $P = 0.18$ and $r = -0.26$; $P = 0.17$, respectively). Therefore, although we cannot exclude a contribution of blood pressure to the endothelial function of previous Gh patients, it is likely that this contribution could be minimal.

Several metabolic and hormonal variables are known to affect vascular reactivity (22, 23). Therefore, we analyzed carbohydrate metabolism, androgens, lipid panel, blood pressure, and homocysteine to assess which of these play a major role in the endothelial dysfunction displayed by women with previous Gh.

Increased resistance to insulin action is a well-established cardiovascular risk factor (24). The molecular pathways by which insulin resistance impairs endothelial function are not completely clear; however, oxidative stress and inflammation may act synergistically, leading to a reduced expression of endothelial nitric oxide synthase (25, 26). As previously observed (1), we found increased insulin resistance in Gh women, slightly during pregnancy (based on glucose area during oral glucose tolerance test in 21 women) and marked after pregnancy, with an 80% higher HOMA and a 60% higher fasting insulin in previous Gh subjects compared with

TABLE 3. Stepwise regression analysis for the relationship between testosterone, HOMA, and HDL-cholesterol and the percent increase in flow-mediated vasodilation ($n = 30$)

	Regression coefficients	R^2	P
Independent variables			
Testosterone	-18.18 ± 5.23	0.34	0.0005
HOMA	-1.28 ± 0.39	0.56	<0.0001
HDL	0.14 ± 0.08	0.59	<0.0001
Intercept	14.37 ± 1.31		

controls. Interestingly, the two measurements of insulin resistance during and after pregnancy had a positive correlation, although it was not significant ($r = 0.41$; $P = 0.06$). Similar metabolic alterations have been shown in previously preeclamptic women (7), supporting the idea that hypertension during pregnancy *per se* is a risk factor for insulin resistance in later life. Both HOMA and fasting insulin showed significant negative correlations with FMD. Interestingly, the relation between FMD and HOMA was independently maintained even after adjusting for the other parameters studied; it was able to explain 22% of the variance in FMD. Thus, although we did not provide data about the mechanistic link between endothelial function and insulin resistance, our finding confirms the association between endothelial dysfunction and insulin resistance in premenopausal healthy women with a history of Gh.

In women, hyperandrogenemia acts as a cardiovascular risk factor. Epidemiological evidence shows that subjects with polycystic ovary syndrome who displayed elevated androgen levels are at greater risk of developing cardiovascular disease (27–29). The reason of this augmented risk has not been well elucidated. However, the direct association among testosterone, insulin resistance, and impaired endothelial function in polycystic ovary syndrome that we and others have described seems to suggest that metabolic and hormonal impairment can play a role in it (30–33). Although in the normal range, the levels of both total and free testosterone of women with previous Gh were significantly higher than those of controls ($P = 0.0012$ and $P = 0.0025$, respectively). This result is consistent with the evidence of augmented androgen levels during and after pregnancy in women with preeclampsia (34–36). Interestingly, the testosterone value was coupled with HOMA ($r = 0.37$; $P = 0.04$), and both were the major independent determinant of endothelial function, as shown by the multivariate analysis in which testosterone was able to explain 34% of the variance in FMD. To the best of our knowledge, this is the first report about the association between mild hyperandrogenemia and endothelial dysfunction, and although our data do not give any precise threshold values for definitively vasotoxic levels of androgens in women, this result suggests that testosterone may act as a cardiovascular risk factor in apparently healthy women with no clinical signs of hyperandrogenemia.

In accord with our preceding results obtained during Gh, women with a history of Gh had higher FFA values than controls. Increased FFA levels are known to negatively affect endothelial function (37). Therefore, it is possible that the moderate increase observed in the previous Gh group could influence vascular reactivity. However, given that we did not observe a significant correlation between FMD and FFA, it is likely that the influence of FFA on endothelial function could be minimal. HDL cholesterol is the antiatherogenic lipoprotein and appears to modulate endothelial function in a beneficial fashion (38). It is well recognized that low HDL cholesterol is associated with increased cardiovascular risk (38). In our study, we found 21% lower HDL levels in previous Gh women compared with controls ($P = 0.0017$). In addition, HDL values correlated with FMD. This relation was independently maintained after adjusting for the other parameters studied, and it was able to explain 3% of the vari-

ance in FMD. Thus, low HDL cholesterol levels appear to negatively affect endothelial function not only in the high degree of reduction seen during experimental studies (39), but also in its relatively moderate decrease exhibited by healthy subjects with previous Gh.

There were some potential limitations to our study. The groups studied were not matched for gestational age at delivery. Given that controls did not deliver at a similar gestational age as Gh women, we do not know whether some control subjects destined to have preeclampsia or Gh during the last phase of gestation avoided it by being delivered earlier. A case-control study with groups matched for all demographic and pregnancy characteristics would be a stronger design. Furthermore, our study had a low power to detect differences between groups in some of the variables analyzed, in particular, fasting glucose and SHBG. We have to underline, however, that the sample size was calculated to have at least 80% power to detect a difference in FMD between groups.

In conclusion, this study provides evidences that women with previous Gh are characterized by endothelial dysfunction and early derangement of carbohydrate, lipid, and hormonal metabolism. Given the known role that these factors have in cardiovascular disease, these findings could explain, at least in part, the clinical and epidemiological findings of augmented cardiovascular disease in subjects with previous pregnancy complicated by Gh.

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