Endothelial Dysfunction
A Link Among Preeclampsia, Recurrent Pregnancy Loss, and Future Cardiovascular Events?

Alfredo M. Germain, Mary Carmen Romanik, Irene Guerra, Sandra Solari, María Soledad Reyes, Richard J. Johnson, Karen Price, S. Ananth Karumanchi, Gloria Valdés

Abstract—We tested the hypothesis that endothelial dysfunction could cause placentation-related defects, persist after the complicated pregnancy, and probably cause cardiovascular disease later in life. Brachial arterial reactivity and factors related to endothelial dysfunction, such as circulating cholesterol, uric acid, nitrites, L-arginine, asymmetrical dimethylarginine, vascular endothelial growth factor, and soluble vascular endothelial growth factor receptor-1, in women with previous healthy pregnancies (n=22), patients with severe preeclampsia (n=25), or patients with recurrent pregnancy loss (n=29), at day 10 of the luteal phase of an ovulatory cycle an average of 11 to 27 months after pregnancy were evaluated. Both groups with placentation defects had a significant decrease in endothelium-dependent dilatation, a higher rate of endothelial dysfunction, lower serum nitrites, and higher cholesterol as compared with control subjects; subjects with previous preeclampsia additionally had higher normal blood pressures and a greater parental prevalence of cardiovascular disease. Patients with recurrent pregnancy loss also demonstrated a significantly lower endothelium-independent vasodilatation. A trend to an inverse correlation was found between serum cholesterol serum and endothelial-mediated vasodilatation in the whole study population. Uric acid, L-arginine, asymmetrical dimethylarginine, vascular endothelial growth factor, and soluble vascular endothelial growth factor receptor-1 were similar in all of the groups. We postulate that endothelial dysfunction may represent a link between preeclampsia and increased cardiovascular disease latter in life and propose that women with unexplained recurrent miscarriages are also at increased cardiovascular risk. The identification and correction of endothelial dysfunction detected during the reproductive stage on obstetric outcome and on cardiovascular diseases needs to be elucidated. (Hypertension. 2007;49:90-95.)

Key Words: endothelial dysfunction ■ endothelium-mediated vasodilatation ■ pregnancy ■ preeclampsia ■ recurrent abortion ■ cardiovascular risk

Preeclampsia not only elevates obstetric morbidity and mortality, but also places the mother at increased risk for developing cardiovascular disease (CVD) later in life. Indeed, subjects with preeclampsia are susceptible to hypertension, obesity/metabolic syndrome, and to CVD particularly if the preeclampsia is complicated by preterm birth.1–4 Interestingly, subjects with recurrent spontaneous abortions have also been reported to be at increased risk for the development of cerebrovascular disease later in life.5 This suggests that there may be underlying risk factors of CVD that predispose to both preeclampsia and/or spontaneous abortions, 2 conditions that represent different degrees of placentation defects.

One potential unifying mechanism could involve the presence of endothelial dysfunction before the obstetric complication. Maternal endothelial dysfunction could impair the invasion of extravillous trophoblasts into the spiral arteries, necessary to create the high-flow, low-resistance uteroplacental vascular system that provides adequate blood supply for fetal growth.6 In turn, endothelial dysfunction has been shown to precede the development of hypertension and metabolic syndrome in several studies.7–9 Moreover, recent studies suggest that endothelial dysfunction occurs far from a preeclamptic pregnancy10–12 and during childhood in low birth–weight infants,13 who are also susceptible to hypertension and CVD later in life.14–16

We hypothesized that endothelial dysfunction should be present in subjects with preeclampsia and with recurrent abortions after their complicated pregnancy and before the development of CVD, whereas women who had previously healthy pregnancies would have a normal endothelial func-
function.27 Subjects with thrombophilia were excluded, with the exception of the antiphospholipid syndrome diagnosed by antiphospholipid antibodies in 8 subjects, 4 belonging to the severe preeclampsia group and 4 to the recurrent abortion group.

Because it is difficult to separate the alterations that predate preeclampsia from those caused by the severe maternal systemic derangement provoked by the ischemic placenta,22,23 idiopathic recurrent pregnancy loss presents as a clinical model of a placental defect devoid of the hypertensive phase of placental ischemia.

We report that patients with a previous history of severe preeclampsia have higher blood pressure, lower endothelium-mediated vasodilatation, increased rates of endothelial dysfunction, decreased plasma nitrates, increased cholesterol levels, and parental CVDs, whereas patients with idiopathic pregnancy loss share with preeclamptic subjects these risk factors, with the exception of increased blood pressure and parental CVDs. These data support a link between placentaion relation disorders and CVD and suggest that placentaion related disorders may constitute an early expression of cardiovascular risk factors.

### Methods

The study was performed between January 1999 and June 2003 in one of the out patient clinics of the Catholic University School of Medicine following a study protocol approved by the institutional review board. All of the patients gave their informed consent. Maternal and perinatal outcomes definitions were those used by the American College of Obstetrics and Gynaecology guidelines.24 Control subjects were normotensive women who gave birth to healthy infants with adequate weight for gestational age and had no miscarriages or preeclamptic pregnancies before the index pregnancy. Severe preeclampsia was defined by one of the following: hypertension >160/110 mm Hg, 24-hour proteinuria >5 g per 24 hours, oliguria <500 mL per 24 hours, cerebral or visual disturbances, pulmonary edema, epigastric or right-upper–quadrant pain, or impaired liver function and thrombocytopenia developing after 20 weeks of gestation in a previously normotensive woman. Eclampsia was defined by the presence of new-onset seizures in a preeclamptic patient. Abruptio placenta, included only when graded as 2 or 3 (associated with vaginal bleeding or concealed hemorrhage, uterine tenderness, and fetal distress), was diagnosed clinically. The hemolysis, elevated liver enzymes, and low-platelet (HELP) syndrome was diagnosed by the combination of hemolysis (lactic dehydrogenase >600 IU/L, serum bilirubin >1.2 mg/dL, or the presence of schistocytes in the peripheral blood), increased serum aspartate aminotransferase concentrations (>70 IU/L), and thrombocytopenia (platelet count <100 000/mm³). Fetal growth restriction was defined by a birth weight below the 10th percentile for the gestational age. Recurrent pregnancy loss required ≥2 sequential spontaneous miscarriages presenting normal placental karyotype and had neither acute placental inflammation nor uterine, thyroid, ovarian, adrenal, or pituitary abnormalities.

Obesity, overweight, chronic hypertension, diabetes, renal and CVDs, and multiple pregnancies in the index pregnancy were exclusion criteria for case and control subjects, because these conditions increase the incidence and the severity of PE.23 Smokers were also excluded, because in them the risk of preeclampsia seems to be reduced26 and, in postpartum, they alter markers of endothelial function.17 Subjects with thrombophilia were excluded, with the exception of the antiphospholipid syndrome diagnosed by antiphospholipid antibodies in 8 subjects, 4 belonging to the severe preeclampsia group and 4 to the recurrent abortion group.

The study was performed on day 10 of the luteal phase of the ovulatory cycle in 74 subjects (71 Hispanics, 2 whites, and 1 Asian), 22 with normal reproductive outcome, 25 with previous severe preeclampsia, and 29 with recurrent pregnancy loss. Women with previous preeclampsia were evaluated after a minimum of 4 months from their last delivery and those with recurrent pregnancy after a minimum of 3 months after their last miscarriage. None used hormonal or intrauterine contraceptives or received medications. Their clinical characteristics, the interval between the index gestation and the study, and data from their previous reproductive history are described in Table 1 and 2. A detailed parental history of cardiovascular disorders was obtained using a structured interview questionnaire. As significant end points of CVD, hypertension and premature atheromatous arterial disease (cerebral, carotid, coronary, aortic, and peripheral) were considered positive. All of the study subjects had ≥12 years of education and belonged to the middle- and high-income groups.

Blood pressure was recorded in the lying position in the right arm with a blood-pressure monitor (Dynamap Compact TS plus, Johnson and Johnson) at 2-minute intervals, and the mean of 3 determinations was used for the statistical analysis. Serum uric acid and cholesterol

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**TABLE 1. General Characteristics in Controls and Patients With Previous Severe Preeclampsia and Recurrent Pregnancy Loss**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n=22)</th>
<th>Severe Preeclampsia (n=25)*</th>
<th>Recurrent Pregnancy Loss (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>32±1.1</td>
<td>31.4±1.2</td>
<td>33.9±0.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.6±0.5</td>
<td>24.5±0.9</td>
<td>23.5±0.6</td>
</tr>
<tr>
<td>Maternal birth weight, g</td>
<td>3086±78</td>
<td>2941±154</td>
<td>3314±138</td>
</tr>
<tr>
<td>Interval from last delivery, months</td>
<td>27±6.9</td>
<td>16±3.5</td>
<td>11±2.2</td>
</tr>
<tr>
<td>Previous pregnancies, n</td>
<td>1.4±0.2</td>
<td>2.0±0.2</td>
<td>3.8±0.3</td>
</tr>
<tr>
<td>Primiparous/multiparous, n</td>
<td>16/6</td>
<td>17/8</td>
<td>0/36</td>
</tr>
<tr>
<td>Previous deliveries, n</td>
<td>1.4±0.2</td>
<td>2.0±0.2</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Previous miscarriages, n</td>
<td>0</td>
<td>0.2±0.1</td>
<td>2.9±0.2</td>
</tr>
<tr>
<td>Newborn weight, g†</td>
<td>3409±69</td>
<td>1,471±140</td>
<td></td>
</tr>
<tr>
<td>Gestational age at delivery/abortion, wk†</td>
<td>38.2±0.2</td>
<td>30.9±0.8</td>
<td>8.1±0.5</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM.

*One patient presented with abrupto placenta, 2 with HELPP syndrome, 2 with eclampsia, 6 with stillbirths, and 14 with intrauterine growth retardation; 2 of the multiparous preeclamptics had a recurrent PE.

†Referred to the index pregnancy.
TABLE 2. Clinical and Biochemical Characteristics of Control Subjects and Patients With Previous Severe Preeclampsia and Recurrent Pregnancy Loss

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n = 22)</th>
<th>Severe Preeclampsia (n = 25)</th>
<th>Recurrent Pregnancy Loss (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>107±2.1</td>
<td>124±2.5</td>
<td>118±2.1</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>59±1.5</td>
<td>73±2.2*</td>
<td>63±1.5</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>74±1.8</td>
<td>90±2.2*</td>
<td>78±1.6</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±2.4</td>
<td>75±2.5</td>
<td>75±2.4</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>168±6.7</td>
<td>201±7.1*</td>
<td>193±6.7*</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>4.2±0.2</td>
<td>4.2±0.2</td>
<td>4.2±0.3</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. *P<0.05 vs control group by ANOVA and posthoc test.

were measured in an automated analyser (Roche Diagnostics, GmbH) in a fasting blood sample.

Brachial artery reactivity was assessed after a 12-hour fast, preceded by a low-fat dinner, as described by Celermajer et al and as reported recently in the Chilean population by our group.28 All of the examinations were performed between 8:00 AM and 11:00 AM after 15 minutes of supine rest. The left brachial artery was scanned longitudinally with a 10-MHz linear transducer (GAIA 8800 MT Medison, Korea and Voulson V730, Medison), and the end-diastolic diameter was measured by the distance between the junctions of the media and adventitia. After 2 initial recordings, a blood-pressure cuff was added, and optical density was determined at 450 nm. All of the assays were done in duplicate, and the protein levels were calculated using a standard curve derived from known concentrations of the respective recombinant proteins.

Nitrates were determined in serum by chemiluminescence using a Sievers Instruments NO analyzer as described previously.17 Briefly, samples were injected into a purge vessel containing vanadium, which converted nitrates and nitrates into NO. The NO was then propelled by the inert gas nitrogen into a reaction chamber where NO was oxidized into NO2 by ozone. The chemiluminescence associated with this reaction was read in millivolts and recorded as a deflection on a data recorder. The area under the curve reflected the NO content in the samples. This was read initially as luminescence units, which, when divided by the slope of a standard curve, gave the precise NO content. Every sample was measured at least twice and the mean taken as representative of the NO content. The measurements were converted to micromoles of NO per liter.

Data are presented as mean±SEM. Data were analyzed by ANOVA, posthoc tests, Student t test, and χ2 test, using Sigma Stat software (Sigma). A P value <0.05 was considered significant.

Results

Patients with previous severe PE and with recurrent pregnancy loss showed a significant decrease in endothelial-dependent dilation, a higher rate of endothelial dysfunction compared with controls, and lower serum nitrite levels (Figure and Tables 3 and 4). Of 8 patients with positive antiphospholipid antibodies, only 2 subjects, 1 in each group with placentaion-related defects, had endothelial dysfunction.

Uterine artery resistance, determined to test whether the previous placentaion related disorders were associated with a persistent local increased vasoconstriction, was evaluated by transvaginal ultrasonography performed between 8:00 AM and 12:00 PM, using a GAIA 8800 MT and Voluson V730 (Medison) with a 5-MHz transvaginal phase array transducer as described by others.30 Uterine artery resistance index represents the mean of right and left uterine arteries. Endometrial width was determined by echography at the end of the examination.

l-arginine and ADMA plasma determination were performed in blood that was extracted in EDTA containing tubes, centrifuged, and its plasma stored frozen at −70°C until assay. Plasma levels of l-arginine and ADMA were measured by high-performance liquid chromatography (HPLC) with fluorescence detection with Millenium 32 software (Waters Corporation) for instrument control and chromatography (HPLC) with fluorescence detection with Millenium 32 software (Waters Corporation) for instrument control and data acquisition, adapted from Pi et al31 and Teerlink et al. Briefly, 0.2 mL of plasma were extracted using MCX OASIS cation exchange columns (Waters Corporation), derivatized with AccQ Fluor Reagent kit, and the derivatives were separated by HPLC using a C18 column (Beckmann, 4.5×250 mm, 5-µm particle size) with a Bio-Rad reverse-phase microguard column and monitored by fluorescence detection. l-arginine, homoarginine as internal standard, and ADMA were eluted at 15, 23, and 30 minutes, respectively. The recovery of l-arginine and ADMA was 90±7.3% (SEM) and 89±3.1%, respectively. Accuracy, expressed as recovery of added analyte from spiked plasma samples (n=5), was 107% and 108% for l-arginine and ADMA, respectively. The intra-assay and interassay coefficients of variation were 3.9% and 9.8% for l-arginine and 9.9% and 8.9% for ADMA.

VEGF and sFlt-1 serum measurements were performed by ELISA according to the manufacturer’s instructions (R&D Systems). Briefly, samples diluted in 0.1% BSA/Trits-buffered saline were incubated in a 96-well plate precoated with a capture antibody directed against VEGF or sFlt1 for 2 hours. The wells were then washed 3 times in 0.05% Tween 20PBS and incubated with a secondary antibody against VEGF or sFlt1 conjugated to horseradish peroxidase for 2 additional hours. The plates were washed again 3 times, substrate solution containing H2O2 and tetramethylbenzidine was added, and optical density was determined at 450 nm. All of the assays were done in duplicate, and the protein levels were calculated using a standard curve derived from known concentrations of the respective recombinant proteins.

Nitrates were determined in serum by chemiluminescence using a Sievers Instruments NO analyzer as described previously.17 Briefly, samples were injected into a purge vessel containing vanadium, which converted nitrates and nitrates into NO. The NO was then propelled by the inert gas nitrogen into a reaction chamber where NO was oxidized into NO2 by ozone. The chemiluminescence associated with this reaction was read in millivolts and recorded as a deflection on a data recorder. The area under the curve reflected the NO content in the samples. This was read initially as luminescence units, which, when divided by the slope of a standard curve, gave the precise NO content. Every sample was measured at least twice and the mean taken as representative of the NO content. The measurements were converted to micromoles of NO per liter.

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Serum cholesterol was significantly elevated in women with previous preeclampsia and with recurrent abortion. A trend to an inverse correlation was found between serum cholesterol levels and endothelial-mediated vasodilatation (r=−0.267; P=0.069) in the whole study population. Uric acid (Table 2), l-arginine, ADMA, VEGF, and sFlt1 were similar in all of the studied groups (Table 4).

Patients presenting with previous PE had a higher, although normal, diastolic and mean blood pressure than control subjects or patients with previous recurrent pregnancy loss (Table 2). Their parental history of CVD showed a higher frequency of CVDs (χ2=7.4, P<0.01 and χ2=4.7, P<0.05 for hypertension and premature atheromatous disease, respectively; Table 5). On the other hand, all of the groups had similar birth weights (Table 1). No significant differences in uterine artery resistance index were observed among the 3 study groups (data not shown), and subjects with recurrent miscarriages had decreased endometrial width (8.0±0.3 versus 9.3±0.6 and 10.1±0.5 mm for the remaining 2 groups).

Discussion

We tested the hypothesis that endothelial dysfunction would be increased in subjects with previous severe preeclampsia, or
Germain et al  Endothelial Dysfunction, PE, and Miscarriage

TABLE 3. Endothelial Function in Controls and Patients With Previous Severe Preeclampsia and Recurrent Pregnancy Loss

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=22)</th>
<th>Severe Preeclampsia (n=25)</th>
<th>Recurrent Pregnancy Loss (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial artery basal diameter, mm</td>
<td>0.30±0.01</td>
<td>0.31±0.01</td>
<td>0.30±0.01</td>
</tr>
<tr>
<td>Endothelium-dependent vasodilatation, %</td>
<td>10.9±0.8</td>
<td>6.4±1.3*</td>
<td>5.7±1.1†</td>
</tr>
<tr>
<td>Endothelium-independent vasodilatation, %</td>
<td>30.0±1.67</td>
<td>25.6±2.65</td>
<td>23.8±1.98*</td>
</tr>
<tr>
<td>Subjects with endothelial dysfunction, %</td>
<td>4.5</td>
<td>40‡</td>
<td>45‡</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. *P<0.05 and †P<0.01 by ANOVA and posthoc test; χ²=8.20 and 10.19; ‡P<0.01 for preeclamptic subjects and recurrent pregnancy groups vs control subjects.

tip phospholipid syndrome, had “pure” preeclampsia or recurrent abortions who otherwise had no evidence for CV risk.

Our primary finding was the endothelial dysfunction was present far from pregnancy in ~50% of subjects with recurrent abortions or with a history of previous severe preeclampsia, and this could not be attributed to changes in maternal birth weight, antiphospholipid antibodies, uric acid, 1-arginine, ADMA, VEGF, or sFlt-1 levels. Although endothelium-mediated vasodilatation and serum cholesterol showed a trend to correlate negatively, this association did not attain statistical significance. Because a negative nonsignificant correlation between total cholesterol and triglycerides has been found in nonpregnant women of similar age,33 further studies, including fractioned/oxidized lipoproteins, deserve to be performed. In addition, women with both types of placental defects had decreased flow-mediated vasodilatation and lower nitrite and higher cholesterol serum levels, whereas the PE group presented higher arterial blood pressures within the normotensive range and a greater prevalence of parental hypertension and premature atheromatous disease than control subjects or subjects with recurrent miscarriages.

Interestingly, there were differences in measurements of endothelial function between preeclamptic subjects and those with recurrent abortions. Although both demonstrated impaired brachial reactivity and lower nitrite levels, suggestive of a defect in endothelial NO release, only endothelium-independent vasodilatation attained a significant decrease in
the group with recurrent abortions. In this last group, the precocity and intensity of the clinical expression of the placentation defect and the decreased vascular smooth muscle dilatation and endometrial width may be consequences of an increased vascular damage not yet expressed by higher arterial blood pressure.

Subjects with preeclampsia frequently have elevated blood levels of uric acid, sFlt-1, and ADMA, and it has been proposed that all 3 factors have a role in the endothelial dysfunction and vascular injury that accompanies the clinical expression of this condition. However, an important finding in this study was that none of these factors were elevated after pregnancy despite the persistence of endothelial dysfunction. This supports the notion that hyperuricemia results from the decreased renal excretion that occurs secondary to pre-eclampsia, whereas ADMA and sFlt-1 derive from the ischemic placenta, and that in parturum, other factors are causing the persistent endothelial dysfunction. It is important to consider that we excluded subjects who had a previous obesity or hypertension, who are at increased risk for developing preeclampsia. It is quite possible that, in those subjects, endothelial dysfunction may be driven by cholesterol, uric acid, and ADMA, which might continue to be expressed after pregnancy. Future studies will have to address this possibility.

One possibility is that the subjects with placentation defects may represent an extreme of the normal Gaussian curve for endothelial function and that it is this latter group that is most predisposed to preeclampsia and or recurrent abortions and future CV disease. Although variants in endothelial NO synthase expression have not been conclusively related to preeclampsia, it remains to be elucidated whether in subjects selected according to the presence of endothelial dysfunction mutations in NO synthase coding genes prevail.

The greater prevalence of parental hypertension in the patients having previously suffered a preeclamptic pregnancy could be biased by the fact that the hypertensive pregnancy could render a family group more sensitive to recall/detect hypertension. However, this observation is consistent with other published studies and with the facts that preeclamptic subjects also had an increased prevalence of parental premature CVD and that women with recurrent abortion double the prevalence of parental hypertension in controls, without attaining statistical significance. The association between preeclampsia and parental history of CVDs may reflect a link among genetic, biochemical, environmental, and behavioral components, which predispose an individual to higher blood pressure and atheromatous disease.

Our data provide further evidence of functional, biochemical, and familial cardiovascular risk markers that may contribute to later CVD in women presenting with severe preeclampsia, as demonstrated by increasing epidemiological studies. Moreover, it adds women with recurrent abortion as a potential population at CV risk, supporting the study by Pell et al, which demonstrated in them an independent association with cerebrovascular disease. The need to identify whether this association may be extrapolated to moderate preeclampsia deserves to be addressed.

In conclusion, endothelial dysfunction, characterized by a lower endothelium-mediated vasodilatation and lower blood nitrites, is present in a significant number of subjects with a history of severe preeclampsia and spontaneous recurrent abortions. We suggest that endothelial dysfunction may be a triggering mechanism for both these pregnancy-associated complications, as well as for future risk for CV disease. The presence of the vascular abnormalities in women with recurrent miscarriage, who were not exposed to the vascular damage of an established PE, supports the hypothesis that, in a subgroup of women, endothelial dysfunction constitutes a cause of placentation defect, which in PE is later aggravated by the factors liberated by the ischemic placenta into the maternal circulation. Although speculative, we postulate that an adequate maternal endothelial function represents a prerequisite for the reception of the invasive trophoblasts by the spiral arteries, which modify their morphology and replace their endothelium. A spiral artery healthy endothelium supposedly constitutes the target of the vasodilator factors synthesized by approaching trophoblasts (NO, bradykinin, and angiotensin-(1–7) among others).

**Perspectives**

The findings of the present study lead to the exciting hypothesis that correction of the endothelial dysfunction early in pregnancy may help prevent obstetric complications derived from placentation-related disorders and eventually may modify the cardiovascular risk later in life. We have reported recently that patients with endothelial dysfunction detected preconceptionally or in early pregnancy have significant improvement of their reproductive outcome when supplemented with L-arginine during pregnancy. We need to pursue studies to test whether endothelial dysfunction represents a cause of placentation defects, identify obstetric patients who present intragestationally or in previous pregnancies with clinical signs of a defective placentation, and introduce interventions to improve endothelial function.

**Acknowledgments**

The authors are indebted to MEGODUC (Médicos Gineco-Obstetras Universidad Católica) for their valuable support in the use of ultrasound facilities for the present study. In addition we thank the colleagues who referred some of the study subjects.

**Sources of Funding**

This study was supported by Fondecyt 1980958 and Gynopharm Division of Recaline Pharmaceutical Company.

**Disclosures**

None.

**References**

Germain et al

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Hypertension. 2007;49:90-95; originally published online November 20, 2006; doi: 10.1161/01.HYP.0000251522.18094.d4

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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