Published in final edited form as:

J Ultrasound Med. 2010 July ; 29(7): 1103–1115.

Should Bilateral Uterine Artery Notching be used in the Risk Assessment for Preeclampsia, Small-for-Gestational-Age, and Gestational Hypertension?

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Abstract

Objective—To determine the value of bilateral uterine artery notching in the second trimester in the risk assessment for preeclampsia, gestational hypertension, and small-for-gestational age (SGA) without preeclampsia.

Methods—This prospective cohort study included 4,190 singleton pregnancies that underwent ultrasound examination between 23–25 weeks of gestation. The 95th percentile of the mean pulsatility index (PI) and resistance index (RI) of both uterine arteries were calculated. Multivariable logistic regression analyses were performed to determine if bilateral uterine artery notching is an independent explanatory variable for the occurrence of preeclampsia, early-onset preeclampsia (≤ 34 weeks), late-onset preeclampsia (> 34 weeks), gestational hypertension and delivery of an SGA without preeclampsia, while controlling for confounding factors.

Results—1) The prevalence of preeclampsia, early-onset preeclampsia, late-onset preeclampsia, SGA and gestational hypertension were 3.4%, 0.5%, 2.9%, 10%, and 7.9%, respectively; 2) 7.2% of the study population had bilateral uterine artery notching; 3) bilateral uterine artery notching was an independent explanatory variable for the development of preeclampsia [odds ratio (OR) 2.1; 95% confidence interval (CI): 1.28–3.36], early-onset preeclampsia (OR: 4.47; 95% CI: 1.50–13.35), and gestational hypertension (OR: 1.50; 95% CI: 1.02–2.26), but not for late-onset preeclampsia or SGA.

Conclusions—Bilateral uterine notching between 23-25 weeks of gestation is an independent risk factor for the development of early-onset preeclampsia and gestational hypertension. Thus, bilateral uterine artery notching should be considered in the assessment of risk for the development of these pregnancy complications.

Keywords

Small for gestational age; uterine artery Doppler velocimetry; pulsatility index; pregnancy; prediction; early-onset preeclampsia; uteroplacental ischemia

Introduction

Increased impedance to blood flow in the uterine arteries in the second trimester of pregnancy, as determined by Doppler ultrasound parameters, has been used as a screening method for preeclampsia and the delivery of a small-for-gestational age (SGA) neonate.¹⁻¹⁶ However, regardless of the Doppler parameters used, this screening method is associated with low positive predictive values,^{3,4,7,10,17-24} indicating that most patients with a positive test will not develop the disease. Thus, any prophylactic intervention in the screen-positive group would include a large number of patients who would not benefit from these interventions. We have proposed that the conceptual framework to screen for complex diseases, including preeclampsia, preterm parturition, fetal growth restriction and fetal death is inadequate because these pregnancy complications have multiple etiologies and their clinical manifestations may be adaptive in nature.²⁵ Moreover, in some cases, these manifestations may depend on gene-environment interactions. Thus, it is unlikely that a single marker or a combination of them will be associated with a high positive predictive value. In contrast, risk assessment allows for the quantification of the risk of an individual patient for the development of these *Great Obstetrical Syndromes*²⁶ using known and/or novel risk factors.

Several mechanisms of disease have been implicated in the pathophysiology of preeclampsia, including: 1) uteroplacental ischemia;²⁷ 2) immune maladaptation;²⁷ 3) very low-density lipoprotein toxicity;²⁷ 4) genetic imprinting;²⁷ 5) increased trophoblast apoptosis/necrosis;²⁸⁻³⁰ and 6) an exaggerated maternal inflammatory response to deported trophoblast.³¹⁻³⁴ The heterogeneity of the disease is exemplified by the observation that chronic uteroplacental ischemia may be more relevant in the pathogenesis of early-onset preeclampsia than in term preeclampsia.^{35,36} Indeed, abnormal uterine artery Doppler velocimetry in the second trimester is associated with a higher risk to develop preeclampsia at <34 weeks than at ≥34 weeks.^{3,7,10,13} Moreover, early-onset preeclampsia is more severe³⁷ and has a higher proportion of growth-restricted fetuses,³⁷ a higher risk for maternal death,³⁸ and a higher frequency of placental pathology^{39,40} than late-onset preeclampsia.

The presence of bilateral uterine artery notching in the second trimester is also associated with an increased risk to develop preeclampsia and for the delivery of an SGA neonate.^{1-5,7-11,13-16} However, due to the subjectivity in ascertaining the presence of early diastolic notching and its limited contribution in the screening for these pregnancy complications,^{10,14} some authors have restricted their use. Thus far, uterine artery notching has been evaluated in the context of screening for preeclampsia and SGA but not for the assessment of risk for the development of these pregnancy complications. The objective of this study was to determine if bilateral uterine artery notching in the second trimester is an independent factor in the risk assessment for preeclampsia, gestational hypertension, and SGA in patients without preeclampsia.

Materials and Methods

Study design and definitions

A prospective cohort study was conducted between December of 1998 and October 2006 to examine the relationship between bilateral uterine artery notching, alone or in combination with other Doppler parameters, and the development of preeclampsia, gestational hypertension and a delivery of an SGA neonate. Gestational age was determined by the last menstrual period or by ultrasound in case the ultrasonographic determination of gestational age was not consistent with the menstrual dating by >2 weeks. Gestational hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg at least on two determinations four hours to one week apart. Preeclampsia was diagnosed in the presence of gestational hypertension and proteinuria (≥ 300 mg in a 24-hour urine collection or at least one dipstick measurement $\geq 2+$) according to ACOG⁴¹ and the National High Blood Pressure Education Program.⁴² Patients with preeclampsia were sub-classified as either early-onset (≤ 34 weeks) or late-onset (> 34 weeks) disease according to the gestational age at which preeclampsia was diagnosed. Small-for-gestational-age was defined as a birthweight (BW) $< 10^{\text{th}}$ percentile for the gestational age at birth according to the national birth weight distribution of a Hispanic population.⁴³ All patients included in this study are of Hispanic origin. Patients with chronic hypertension, multiple pregnancies, fetal anomalies, pre-gestational diabetes mellitus or cardiac disease were excluded from the study.

All patients provided written informed consent before participating in the study. The use of clinical and ultrasound data for research purposes was approved by the Human Investigation Committee of the Sotero del Rio Hospital, Santiago, Chile (an affiliate of the Pontificia Catholic University of Santiago, Chile), and the Institutional Review Board of the National Institute of Child Health and Human Development of the National Institute of Health (NIH/DHHS).

Uterine artery Doppler velocimetry

Five experienced sonographers performed Doppler ultrasound of the uterine arteries between 23 to 25 weeks of gestation using real-time ultrasound equipment ACUSON 128-XP (ACUSON Corporation, Mountain View, CA, USA) with a 3.5 MHz or a 5 MHz curvilinear probe. The right and left uterine arteries were identified in an oblique plane of the pelvis at the crossover with the external iliac arteries and the Doppler signals were sampled. When three similar consecutive waveforms were obtained, the pulsatility index (PI) and resistance index (RI) of the right and left uterine arteries were measured, and the mean PI or mean RI of the two vessels were calculated. The presence of an early diastolic notch in the uterine arteries was determined using the criteria proposed by Bower et al.¹⁹ A sub-analysis confined to patients who underwent Doppler ultrasound of the uterine arteries at ≥ 26 weeks of gestation was performed to determine if persistence of bilateral uterine artery notching was associated with a higher frequency of the study outcomes.

Study outcomes

The primary outcomes included the development of preeclampsia, early-onset preeclampsia, late-onset preeclampsia, and gestational hypertension, as well as the delivery of an SGA neonate from patients without preeclampsia. Gestational hypertension was included in the outcomes due to its association with adverse pregnancy outcomes⁴⁴ and the possibility that this pregnancy complication may represent an intermediate phenotype in the spectrum of anti-angiogenic states that include preeclampsia and SGA.^{45,46} Secondary outcomes were placental abruption and a composite of severe neonatal morbidity that included

intraventricular hemorrhage, necrotizing enterocolitis and hyaline membrane disease with post-natal sonographic/radiological confirmation.

Statistical analysis

Comparisons between proportions were performed with chi-square, chi-square test for independence or Fisher's exact test. Receiver operating characteristic (ROC) curves were constructed to describe the relationship between sensitivity and the false-positive rate (1-specificity) of bilateral uterine artery notching, alone or in combination with other Doppler parameters, in the identification of patients destined to develop the outcomes. The areas under the curve (AUC) of these Doppler parameters in the prediction of the outcomes were compared.

Multivariable logistic regression analysis was used to explore the relationship between the occurrence of the outcomes and the following explanatory variables: bilateral uterine artery notching, a mean uterine artery PI >95th percentile (mean PI >1.4) or a mean uterine artery RI >95th (mean RI >0.7), maternal age >35 years, previous preeclampsia, nulliparity, first trimester body mass index (BMI) >30 kg/m², and smoking status. The statistical packages used were SPSS v.12.0 (SPSS Inc., Chicago, IL, USA), MedCalc version 7.4.4.1. (MedCalc Software, Belgium) and R (R-2.5.1.tar.gz). A p-value of <0.05 was considered significant.

Results

Prevalence of the outcomes

During the study period, 4,190 women with a singleton pregnancy underwent ultrasound examination between 23-25 weeks of gestation. Of those, 240 women (5.7%) were lost to follow-up; thus 3,950 women were included in the final statistical analyses. The prevalence of preeclampsia, early-onset preeclampsia, late-onset preeclampsia, SGA without preeclampsia, and gestational hypertension were 3.4% (135/3,950), 0.5% (19/3,950), 2.9% (116/3,950), 10% (396/3,950), and 7.9% (311/3,950), respectively. Placental abruption occurred in 0.7% (29/3,950) and a composite of severe neonatal morbidity occurred in 0.6% (22/3,950) of patients. The demographic and clinical characteristics of the study population according to pregnancy outcome are displayed on Tables 1 and 2, respectively. Table 3 displays the odds ratio (OR) and 95% confidence interval (CI) of all the explanatory variables for the occurrence of the primary outcomes of the study.

Diagnostic indices, predictive values and likelihood ratios of bilateral uterine artery notching

Bilateral uterine artery notching was present in 7.2% (284/3,950) of the population between 23 and 25 weeks of gestation. The frequency of this sonographic finding among groups is displayed in Table 1. The diagnostic indices, predictive values and likelihood ratios of bilateral uterine artery notching for the prediction of outcomes are displayed in Table 4. Logistic regression analysis indicated that the presence of this sonographic finding was an independent explanatory variable for the occurrence of early-onset preeclampsia and gestational hypertension, but not for late-onset preeclampsia, SGA in the absence of preeclampsia, placental abruption or a composite of severe neonatal morbidity, after adjusting for a mean PI >95th percentile, maternal age >35 years, previous preeclampsia, nulliparity, smoking, and first trimester BMI >30 (Table 3).

Diagnostic indices, predictive values and likelihood ratios of a mean uterine artery PI or a mean RI >95th percentile

A mean uterine artery PI or a mean RI >95th percentile was present in 5.1% (201/3,950) and 4.9% (195/3,950) of the population, respectively. A mean PI >95th percentile had a higher

area under the curve (AUC: 0.577) than a mean RI >95th percentile (AUC: 0.57) in the prediction of preeclampsia, but the difference was not statistically significant ($p=0.68$) (Figure 1). Logistic regression analysis revealed that a mean uterine artery PI >95th percentile was an independent explanatory variable for the occurrence of preeclampsia, early-onset preeclampsia, late-onset preeclampsia, and SGA without preeclampsia, as well as a composite of neonatal morbidity (OR: 9.1; 95% CI: 3.34-24.62), but not for gestational hypertension or placental abruption, after adjusting for bilateral notching and the other covariates (Table 3). The OR and 95% CI of a mean uterine artery PI >95th percentile in the identification of the primary outcomes are displayed in Table 3, and the diagnostic indices are displayed in Table 5.

Bilateral uterine artery notching and/or a mean uterine artery PI >95th percentile in the identification of the outcomes

The presence of bilateral uterine artery notching and/or a mean uterine artery PI >95th percentile had the highest area under the curve for the prediction of preeclampsia (AUC: 0.619) and early-onset preeclampsia (AUC: 0.821) than the other Doppler parameters (Figures 1 and 2, respectively). However, the area under the curve of the combination of these Doppler parameters was only significantly larger than that of bilateral uterine artery notching alone in the prediction of preeclampsia ($p=0.02$).

Table 6 displays the diagnostic indices, predictive values and likelihood ratios of the presence of bilateral uterine artery notching and/or a mean uterine artery PI >95th percentile for the identification of the primary outcomes. The presence of bilateral uterine artery notching and/or a mean uterine artery PI >95th percentile was an independent explanatory variable for the identification of patients destined to develop preeclampsia, early onset preeclampsia, late onset preeclampsia, SGA without preeclampsia and gestational hypertension (Table 7), as well as for placental abruption (OR: 3.07; 95% CI: 1.29-7.34) and a composite of neonatal morbidity (OR: 7.34; 95% CI: 3.11-17.32), after adjusting for the other covariates.

Persistent bilateral uterine artery notching in the third trimester and pregnancy outcomes

Uterine artery Doppler velocimetry after 26 weeks of gestation was performed in 30.4% (1,201/3,950) of patients. Patients with persistent bilateral uterine notching had a significantly higher frequency of early-onset preeclampsia ($p=0.003$) as well as a higher composite of severe neonatal morbidity ($p=0.01$) than those with bilateral uterine notching between 23-25 weeks but not in the third trimester (Table 8). Of note, 1.1% (43/1,201) of patients had bilateral uterine artery notching in the third trimester, but not between 23 and 25 weeks. These patients had a similar frequency of late-onset preeclampsia, SGA without preeclampsia and gestational hypertension than those who had bilateral uterine artery notching in the second but not in the third trimester. Moreover, these patients had a higher frequency of preeclampsia ($p<0.001$) than patients without bilateral uterine artery notching in the second or third trimester (Table 8).

Discussion

Main findings of the study

The results of this study indicate that bilateral uterine artery notching between 23 and 25 weeks of gestation is an independent risk factor for the development of both early onset preeclampsia, as well as for the delivery of an SGA neonate. Thus, we propose that bilateral uterine artery notching should be considered in the assessment of risk for these pregnancy complications.

The observation that the presence of bilateral uterine artery notching and/or a mean uterine artery PI > 95th percentile is an independent risk factor for the development of gestational hypertension is novel. This observation provides additional evidence that gestational hypertension may represent an intermediate phenotype between patients who developed preeclampsia and those who did not.⁴⁶ This observation is relevant in view of the association between gestational hypertension and an increased risk for fetal death or severe neonatal morbidity and mortality.⁴⁴

Risk factors for the development of preeclampsia

The independent risk factors for the development of preeclampsia that resulted from the logistic regression analysis (Table 3) are consistent with previous reports⁴⁷⁻⁵⁷ that were summarized in a recent systematic review.⁵⁸ However, maternal age as a continuous or dichotomized variable (>35 years or >40 years) was not an independent explanatory variable for the occurrence of the outcomes. The observation that smoking did not confer a protective effect for the development of preeclampsia (OR: 0.65; 95% CI: 0.33-1.26) may be due to the low prevalence of smoking in the study population.⁴⁶ However, smoking was associated with an increased risk of delivering an SGA neonate in the absence of preeclampsia (OR: 1.40; 95% CI: 1.03-1.90), as previously reported.⁵⁹⁻⁶²

The physiopathology of persistent bilateral uterine notching

Longitudinal studies in uncomplicated pregnancies indicate that diastolic notching in the uterine arteries disappear by the 26th week of gestation.^{63,64} This is consistent with the observation that bilateral uterine artery notching were present in only 5.6% (178/3,153) of patients who did not develop preeclampsia or gestational hypertension and did not deliver an SGA neonate in the absence of preeclampsia. The pathophysiology of the uterine artery diastolic notch is not completely understood. However, two theoretical computer models have been used to explain the presence of uterine artery diastolic notching. Mo et al.⁶⁵ proposed that the notch is the result of a wave reflection due to a high placental bed resistance. In contrast, Talbert et al.⁶⁶ put forward the idea that the uterine artery diastolic notch is due to increased arterial wall compliance. The observation that the high impedance to blood flow in the uterine arteries during labor is not associated with uterine artery notching⁶⁶ supports the latter theory. More recently, Brodzski et al.⁶⁷ reported that bilateral uterine artery notching was not associated with changes in the mechanical properties of large vessels (strain and stiffness), as determined by ultrasound, but with endothelial cell dysfunction as determined by abnormal flow-mediated dilatation of the brachial arteries and low maternal plasma concentrations of nitrites and nitrates. However, the authors did not study the mechanical properties of the uterine arteries, and the study was done on women who remained normotensive throughout pregnancy.

Studies in which gelfoam has been used to embolize the uterine circulation in pregnant animals showed that the presence of uterine artery notching is associated with substantial reduction in the blood flow.^{68,69} Indeed, Ochi et al. reported that progressive embolization of the spiral arteries in pregnant animals produced a diastolic notch only when the uterine blood flow was reduced to approximately one third, and the vascular resistance was increased three to four times the normal values.^{68,69} In an accompanying editorial,⁷⁰ Professor Stuart Campbell praised the contributions of Talbert et al. and Ochi et al. to the understanding of the physiopathology of uterine artery notching while indicating that, in his experience, uterine artery notching is “the most predictive feature of the uterine artery waveform in terms of development of preeclampsia.” Collectively, this evidence indicates that the persistence of uterine artery notching may be associated with a substantial reduction in uterine artery blood flow.

Risk assessment versus screening for complex diseases

We propose that the conceptual framework of prenatal screening for a single-gene disorder such as hemoglobinopathies⁷¹ or specific chromosomal anomalies⁷² can not be applied to complex diseases such as preeclampsia, fetal growth restriction, preterm labor with intact membranes, preterm prelabor rupture of membranes or fetal death. We refer to these diseases as the *Great Obstetrical Syndromes* whose common features include: 1) multiple etiologies; 2) chronicity; 3) fetal involvement; 4) their clinical manifestations may be adaptive; and 5) their occurrence may be due to a gene-environment interaction.^{25,26} Thus, the expectation that a single marker or a combination of them will have a high positive predictive value in the prediction of these syndromes is unrealistic. Indeed, both the results of this study and a large body of evidence^{3,4,7,10,17-24,73} indicate that the positive predictive value of abnormal uterine artery Doppler velocimetry for the prediction of preeclampsia is low, ranging from 8% to 33%.²⁴ Most patients with a positive test will therefore not develop the disease. Moreover, a systematic review conducted by the World Health Organization concluded that there is no clinically useful screening test to predict the development of preeclampsia.⁷⁴ In contrast, risk assessment allows for the quantification of the risk of an individual patient to develop preeclampsia based on known or novel risk factors.

The results of this study indicate that the presence of bilateral uterine artery notching is an independent risk factor for the development of preeclampsia and for the delivery of an SGA neonate in the absence of preeclampsia. These results are consistent with a recent report where a model was constructed using ultrasound, demographic and clinical parameters for the prediction of preeclampsia.¹⁵ However, the model was used in the context of screening for this complex disease, and the positive and negative predictive values were not reported. According to Roberts,⁷⁵ these predictive values should be available to determine the usefulness of a test as predictor of preeclampsia. Indeed, the negative predictive values of second trimester uterine artery Doppler velocimetry for preeclampsia and SGA without preeclampsia are above 97% and 90%, respectively suggesting that patients with normal uterine artery Doppler velocimetry have a very low risk to develop these pregnancy complications. The corresponding negative predictive values of early-onset preeclampsia (>99%) may be a reflection of prevalence of this disease.

Are persistent bilateral uterine artery notching in the third trimester associated with a high rate of adverse pregnancy outcomes?

The data presented in Table 8 indicate that women with bilateral uterine artery notching in both the second and the third trimester had the highest rates of preeclampsia, SGA in patients without preeclampsia, gestational hypertension, and a composite of severe neonatal morbidity. Of note, this longitudinal study identified a novel group of patients who had bilateral uterine artery notching in the third but not in the second trimester. The frequency of the outcomes in this group was similar to that of patients who had bilateral uterine artery notching in the second but not in the third trimester (Table 8). This group of patients may represent women in which an insult to the fetal supply line may have occurred relatively late in the course of pregnancy. This insult was probably severe enough to produce bilateral uterine artery notching. It is unlikely that this group represents women in which the diagnosis of bilateral uterine artery notching was missed in the second trimester, because if this was the case, the frequency of adverse outcomes would be similar to that of patients with bilateral uterine artery notching in the second and third trimesters.

The observation that patients who had bilateral uterine artery notching in the second but not in the third trimester had a higher frequency of preeclampsia and SGA in the absence of preeclampsia than patients who did not have bilateral notching in the second or third trimester is consistent with the report of Campbell et al.⁷⁶ These authors reported that

women whose uterine artery Doppler was abnormal at 20 weeks but normalized between 24 to 26 weeks (“late normalizers”) had a significantly lower birthweight than those with a normal uterine artery Doppler at 20 weeks and between 24 and 26 weeks. Thus, the concept of “late Doppler normalization” could be extended to patients with bilateral uterine artery notching in the second trimester which later resolved.

Conclusions

The presence of bilateral uterine artery notching between 23 and 25 weeks of gestation is an independent risk factor for the development of preeclampsia and the delivery of an SGA neonate in the absence of preeclampsia. Thus, this ultrasound parameter should be considered in the risk assessment for these pregnancy complications. The presence of bilateral uterine artery notching and/or a high mean uterine artery PI confers a very high risk for the development of early-onset preeclampsia and is an independent risk factor for the development of gestational hypertension and placental abruption.

A novel group of patients was identified who had bilateral uterine artery notching in the third but not in the second trimester. These patients have a higher frequency of preeclampsia than patients without bilateral uterine artery notching in the second or third trimester. It is possible that these patients may have had an insult to the fetal supply line late in pregnancy.

Acknowledgments

This research was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

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Figure 1. Comparison of areas under the curve (AUC) of Doppler parameters in the prediction of preeclampsia

The presence of a bilateral uterine artery notching and/or a mean uterine artery PI>95% percentile had the highest auc (0.619) for the prediction of preeclampsia. However, the auc of the combination of these Doppler parameters was significantly higher than that of bilateral notching alone (auc: 0.578; $p=0.02$) but not significantly higher than the combination of bilateral uterine artery notching and/or a mean uterine artery RI>95% percentile (auc: 0.612; $p=0.53$), or a mean uterine artery PI or RI >95% (auc: 0.577, $p=0.05$ and auc: 0.570, $p=0.05$; respectively).

Figure 2. Comparison of areas under the curve (auc) of Doppler parameters in the prediction of early-onset preeclampsia

The presence of bilateral uterine artery notching and/or a mean uterine artery PI or RI > 95% percentile had the highest auc (0.821) for the prediction of early-onset preeclampsia.

However, the auc of the combination of these Doppler parameters was not significantly higher than that of bilateral notching alone (AUC: 0.73; $p=0.07$) or that of a mean uterine artery PI or RI > 95% (auc: 0.767, $p=0.65$ for both comparisons).

Table 1

Demographic and clinical characteristics of the population according to pregnancy complications.

	Normal pregnancy/other complications (n=3,153)	Early-onset Preeclampsia (n=19)	Late-onset Preeclampsia (n=116)	SGA without preeclampsia (n=396)	p
Maternal age (years)	26 (13-46)	25 (15-38)	22 (15-42)	24 (15-46)	<0.001
Nulliparity (%)	35.7 (1,132/3,168)	60 (12/20)	71.8 (84/117)	50 (199/398)	<0.001
Preeclampsia in a previous pregnancy (%)	2.2 (68/3,153)	10.5 (2/19)	5.2 (6/116)	1 (4/396)	NS
BMI>30 (%)	12.6 (396/3,153)	21.1 (4/19)	19 (22/116)	8.1 (32/396)	0.005
Smokers (%)	10.6 (334/3,151)	10.5 (2/19)	6.9 (8/116)	13.8 (55/396)	NS
Bilateral uterine artery notches (%)	5.6 (178/3,153)	52.6 (10/19)	17.2 (20/116)	12.6 (50/396)	<0.001
Mean uterine artery PI >95 th percentile (%)	3.6 (114/3,153)	57.9 (11/19)	13.8 (16/116)	11.6 (46/396)	<0.001
Mean uterine artery RI >95 th percentile (%)	3.7 (116/3,153)	63.2 (12/19)	12.1 (14/116)	9.8 (39/396)	0.001

BMI: body mass index. SGA: small-for-gestational age.

The results are expressed as median (range) or percentage (proportions)

Table 2

Clinical outcomes according to pregnancy complications.

	Normal pregnancy/other complications (n=3,153)	Early-onset Preeclampsia (n=19)	Late-onset Preeclampsia (n=116)	SGA without preeclampsia (n=396)	p
Gestational age at delivery (weeks)	39.6 (25.6-43)	32.4 (27.3-37.1)	38.4 (34.7-42.1)	39.3 (27.4-41.9)	<0.001
Birthweight (grams)	3,450 (870-5,350)	1,460 (860-3,320)	3,155 (1,420-4,580)	2,770 (550-3,070)	<0.001
BW <10 th percentile (%)	0 (0/3,153)	31.6 (6/19)	25 (29/116)	100 (398/398)	<0.001
Placental abruption (%)	0.6 (19/3,153)	5.3 (1/19)	2.6 (3/116)	0.8 (3/396)	NS
Composite of severe neonatal morbidity (%)	0.4 (14/3,153)	26.3 (5/19)	0 (0/116)	0.5 (2/396)	<0.001

BW: birthweight. SGA: small-for-gestational age

The results are expressed as median (range) or percentage (proportions)

Table 3

Logistic regression analysis for the prediction of the study outcomes.

Explanatory variable	Preeclampsia OR (95% CI)	Early-onset PE OR (95% CI)	Late-onset PE OR (95% CI)	SGA without PE OR (95% CI)	Gestational hypertension OR (95% CI)
Maternal age>35 years	1.0 (0.44-2.04)	1.7 (0.33-8.22)	0.85 (0.35-2.02)	1.3 (0.92-1.86)	1.3 (0.91-1.96)
Previous preeclampsia	5.77 (2.49-13.31)	7.5 (1.23-44.76)	5.9 (2.32-14.72)	0.5 (0.18-1.37)	2.8 (1.56-5.02)
BMI>30	2.1 (1.30-3.31)	1.5 (0.42-5.04)	2.2 (1.31-3.55)	0.59 (0.4-0.86)	1.7 (1.23-2.3)
Nulliparity	4.8 (3.11-7.42)	3.0 (0.97-8.94)	5.2 (3.26-8.36)	1.6 (1.27-1.98)	1.8 (1.42-2.36)
Smoking	0.65 (0.34-1.26)	1.04 (0.23-4.79)	0.6 (0.28-1.22)	1.4 (1.03-1.90)	1.2 (0.83-1.70)
Bilateral uterine artery notches	2.1 (1.28-2.36)	4.5 (1.50-13.35)	1.7 (0.99-2.96)	1.4 (1.0-2.03)	1.5 (1.02-2.26)
Mean uterine artery PI >95 th	3.9 (2.32-6.44)	14.5 (4.84-43.36)	2.76 (1.47-4.95)	2.7 (1.86-3.95)	1.3 (0.83-2.15)

PE: Preeclampsia, SGA: small for gestational age, BMI: body mass index, OR: odds ratio, CI: confidence interval

Diagnostic indices of bilateral uterine artery notches in the identification of patients destined to develop preeclampsia and those destined to deliver an SGA neonate without preeclampsia.

Table 4

Outcome	Sensitivity	Specificity	PPV	NPV	LR(+) (95% CI)	LR(-) (95% CI)
Preeclampsia	22.2% (30/135)	93.3% (3,561/3,815)	10.6% (30/284)	97.1% (3,561/3,666)	3.34 (2.38-4.68)	0.83 (0.59-1.17)
Early-onset PE (≤34 weeks)	52.6% (10/19)	93.3% (3,561/3,815)	3.8% (10/264)	99.7% (3,561/3,570)	7.91 (5.08-12.31)	0.51 (0.33-0.79)
Late-onset PE (>34 weeks)	17.2% (20/116)	93.3% (3,561/3,815)	7.3% (20/274)	97.4% (3,561/3,657)	2.59 (1.71-3.93)	0.89 (0.58-1.34)
SGA without preeclampsia	12.6% (50/396)	93.4% (3,320/3,554)	17.4% (50/284)	90.6% (3,320/3,666)	1.92 (1.44-2.56)	0.94 (0.70-1.25)

PE: Preeclampsia, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio SGA: small for gestational age

Table 5

Diagnostic indices of a mean uterine artery PI>95th percentile in the identification of patients destined to develop preeclampsia and those destined to deliver an SGA neonate without preeclampsia.

Outcome	Sensitivity	Specificity	PPV	NPV	LR(+) (95% CI)	LR(-) (95% CI)
Preeclampsia	20% (28/137)	95.4% (3,658/3,834)	13.4% (28/204)	97.1% (3,658/3,767)	4.39 (3.04-6.33)	0.84 (0.58-1.21)
Early-onset PE (≤34 weeks)	57.9% (11/19)	95.4% (3,641/3,815)	5.9% (11/185)	99.8% (3,641/3,649)	12.69 (8.42-12.13)	0.44 (0.29-0.66)
Late-onset PE (>34 weeks)	13.8% (16/116)	95.4% (3,641/3,815)	8.4% (16/190)	97.3% (3,641/3,741)	3.02 (1.88-4.88)	0.90 (0.56-1.46)
SGA without preeclampsia	11.6% (46/396)	95.6% (3,399/3,554)	22.9% (46/201)	90.7% (3,399/3,749)	2.66 (1.95-3.64)	0.92 (0.68-1.26)

PE: Preeclampsia, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio SGA: small for gestational age

Diagnostic indices of the presence of bilateral uterine artery notches and/or a mean uterine artery PI>95th percentile in the identification of patients destined to develop preeclampsia and those destined to deliver an SGA neonate without preeclampsia.

Table 6

Outcome	Sensitivity	Specificity	PPV	NPV	LR(+) (95% CI)	LR(-) (95% CI)
Preeclampsia	33.3% (45/135)	90.5% (3,451/3,815)	11% (45/409)	97.5% (3,451/3,815)	3.49 (2.70-4.52)	0.74 (0.57-0.95)
Early-onset PE (≤34 weeks)	74% (15/20)	90.5% (3,468/3,834)	3.7% (15/381)	99.9% (3,468/3,473)	7.72 (5.80-10.28)	0.29 (0.22-0.39)
Late-onset PE (>34 weeks)	26.7% (31/116)	90.5% (3,451/3,815)	7.8% (31/395)	97.6% (3,451/3,536)	2.80 (2.04-3.84)	0.81 (0.59-1.11)
SGA without preeclampsia	19.4% (77/396)	90.7% (3,222/3,554)	18.8% (77/409)	91% (3,222/3,554)	2.08 (1.66-2.61)	0.89 (0.71-1.11)

PE: Preeclampsia, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio SGA: small for gestational age

Table 7

Logistic regression analysis of the presence of bilateral uterine artery notches and/or a mean uterine artery PI>95th percentile for the prediction of the outcomes adjusted for maternal age, previous preeclampsia, nulliparity, smoking status, and BMI.

Outcome	Bilateral uterine artery notches and/or a mean uterine artery PI >95 th percentile	
	OR	95% C.I.
Preeclampsia	4.0	2.71-5.83
Early-onset PE (≤ 34 weeks)	25.7	9.01-73.31
Late-onset PE (> 34 weeks)	2.9	1.85-4.4
SGA without preeclampsia	2.3	1.72-2.97
Gestational hypertension	1.6	1.18-2.25

PE: Preeclampsia, SGA: small for gestational age, BMI: body mass index, OR: odds ratio, C.I. confidence interval SGA: small for gestational age

Table 8

Clinical outcomes according to the presence of persistent bilateral uterine artery notches in the third trimester.

	No BUN in the second or third trimester (n=1,090)	BUN in the second trimester only (n=43)	BUN in the third trimester only (n=43)	BUN in the second and third trimester (n=25)	p
Preeclampsia	2.8 (31/1,090)	9.3 (4/43)	16.3 (7/43)	36 (9/25)	<0.001
Early-onset PE (≤ 34 weeks)	0.3 (3/1,062)	0 (0/39)	7.7 (3/39)	27.3 (6/22)	<0.001
Late-onset PE (> 34 weeks)	2.6 (28/1,087)	9.3 (4/43)	10 (4/40)	15.8 (3/19)	<0.001
SGA without preeclampsia	9.5 (104/1,090)	16.3 (7/43)	14 (6/43)	36 (9/25)	0.02
Gestational hypertension	7.7 (84/1,090)	14 (6/43)	14 (6/43)	28 (7/25)	0.01
Composite of severe neonatal morbidity (%)	0.2 (2/1,090)	0 (0/43)	2.3 (1/43)	20 (5/25)	0.004

BUN: bilateral uterine artery notches; BW: birthweight. The results are expressed as median (range) or percentage (proportions) SGA: small for gestational age. The p-values are derived using chi-square test for independence.