

INTERRELATIONSHIP AND CLINICAL  
SIGNIFICANCE OF INCREASED  
RESISTANCE IN THE UTERINE  
ARTERIES IN PATIENTS WITH  
HYPERTENSION OR PREECLAMPSIA  
OR BOTH

ALEXANDER D. KOFINAS, MD,  
MARY PENRY, RN, RDMS,  
NICOLAS V. SIMON, MD,

and

MELISSA SWAIN, RN

York, Pennsylvania, and Winston-Salem, North  
Carolina

From York Hospital and Bowman Gray School of Medicine.

Reprinted from  
AMERICAN JOURNAL OF OBSTETRICS AND  
GYNECOLOGY,  
St. Louis

Vol. 166, No. 2, pp. 601-606, February, 1992  
(Copyright © 1992, by Mosby-Year Book, Inc.)  
(Printed in the U.S.A.)

# Interrelationship and clinical significance of increased resistance in the uterine arteries in patients with hypertension or preeclampsia or both

Alexander D. Kofinas, MD, Mary Penry, RN, RDMS, Nicolas V. Simon, MD, and  
Melissa Swain, RN

York, Pennsylvania, and Winston-Salem, North Carolina

**OBJECTIVES:** This study was designed to evaluate the clinical significance of the Doppler flow velocity waveform analysis of the two uterine arteries on an individual basis and in combination expressed as the mean uterine artery.

**STUDY DESIGN:** We evaluated uterine artery resistance by means of continuous wave Doppler ultrasonography in 123 pregnant women with chronic hypertension, preeclampsia, or both. The placental location was determined by real-time ultrasonography. Clinical outcomes were compared according to uterine artery abnormalities. The Doppler flow studies were not used in patient management.

**RESULTS:** In patients with unilateral placentas ( $n = 67$ ) the placental uterine artery was found to be a better predictor of poor pregnancy outcome than the nonplacental artery and the mean of the two arteries. There was a strong degree of correlation between abnormal nonplacental uterine artery and abnormal mean of uterine artery ( $r = 0.75, p < 0.001$ ), and there was a moderate degree of correlation between abnormal placental uterine artery and abnormal mean uterine artery ( $r = 0.46, p < 0.001$ ). Uterine artery discordance (left - right uterine artery systolic/diastolic ratio) was mostly the result of an abnormal nonplacental uterine artery ( $r = 0.74, p < 0.0001$ ) and not the result of an abnormal mean uterine artery ( $r = 0.44, p < 0.003$ ); the degree of discordance did not relate to pregnancy outcome. Unilateral placental location was associated with longer stays in neonatal intensive care units and more perinatal deaths.

**CONCLUSION:** Because of the differences between the two uterine arteries, we conclude that for proper interpretation of uterine artery flow velocity waveforms, the placental location should be known and each vessel analyzed individually. (AM J OBSTET GYNECOL 1992;166:601-6.)

**Key words:** Uterine arteries, hypertension, preeclampsia, Doppler ultrasonography

Intrauterine growth retardation and preeclampsia are both conditions strongly related to proper placental development and function. It has been shown that poor trophoblastic conversion of the spiral arterioles leads to development of intrauterine growth retardation, preeclampsia, or both.<sup>1</sup> Poor trophoblastic conversion results in a decreased uteroplacental vascular capacitance and increased uteroplacental artery resistance. This in turn can lead to decreased uteroplacental bed perfusion, because perfusion is inversely proportional to vascular resistance.

Doppler flow velocity waveform analysis in the uterine arteries performed by continuous wave Doppler ultrasonography is considered a clinically useful method for evaluation of high-risk pregnancies, especially in pregnancies complicated by impaired fetal growth and preeclampsia.<sup>2-7</sup> Some investigators have evaluated only the placental uterine artery and others both uterine arteries collectively. Schulman et al.<sup>8</sup> have shown that

both uterine arteries do not respond to pregnancy with the same degree of compliance and that the difference in the resistance (change in systolic/diastolic ratio) between the two uterine arteries correlated well with poor pregnancy outcome. We have shown that placental location can influence uterine artery resistance.<sup>9</sup> Placental laterality is associated with elevated uterine artery resistance and the development of preeclampsia and impaired fetal growth.<sup>10</sup>

The present study was designed to evaluate the relationship between pregnancy outcome and increased resistance in each uterine artery individually and the interrelationship of the two uterine arteries in relation to clinical outcome in patients with hypertension and preeclampsia or both.

## Material and methods

A total of 160 patients were enrolled in the study. Seventeen were excluded because of incomplete pregnancy outcome information and 20 because the interval from the last study to delivery was  $>10$  days. The study subjects were recruited from a patient population referred to the antenatal testing unit of Forsyth Memorial Hospital for fetal evaluation because of preeclampsia or chronic hypertension. All patients were examined

From York Hospital and Bowman Gray School of Medicine.

Received for publication April 10, 1991; revised July 1, 1991; accepted July 15, 1991.

Reprint requests: Alexander D. Kofinas, MD, York Hospital, 1001 S. George St., York, PA 17405.

6/11/32398

**Table I.** Clinical and Doppler characteristics in seven cases with perinatal mortality

Case No.	Diagnosis	Gestational age at delivery (wk)	Birth weight (gm)	Uterine artery flow velocity waveform	Umbilical artery flow velocity waveform	Location of placenta
1	Chronic hypertension	26	480	Abnormal	Normal	Central
2	Superimposed preeclampsia	28	520	Abnormal	Abnormal	Lateral
3	Preeclampsia	26	560	Abnormal	Abnormal	Central
4	Chronic hypertension	35	588	Abnormal	Abnormal	Lateral
5	Preeclampsia	28	665	Abnormal	Abnormal	Lateral
6	Chronic hypertension	39	3544	Normal	Normal	Lateral
7	Preeclampsia	32	1180	Abnormal	Abnormal	Lateral

\*Electronic fetal monitoring.

after 24 weeks' gestation and no more than 10 days before delivery. Although the majority of the patients underwent more than one evaluation, only the last examination was used in the analysis, because our goal was to examine the relationship of the uterine artery condition to pregnancy outcome as close to delivery as possible. The majority of the patients were inpatients (105) and the rest were outpatients. The physicians involved in the management of the patients were unaware of the Doppler data, and all management decisions were based solely on standard obstetric care practices. The study was approved by the institution's Clinical Research Practices Committee; all patients gave written informed consent.

Diagnosis and classification of the hypertensive disorders were according to criteria established by the American College of Obstetricians and Gynecologists.<sup>11</sup> Patients were considered to have pathologic proteinuria if the total protein level in a 24-hour urine specimen was  $\geq 500$  mg or if a random urine specimen obtained by bladder catheterization had a dipstick value of  $\geq 2+$ . Growth charts appropriate for our population were used to classify the infants as small for gestational age or appropriate for gestational age.<sup>12</sup>

The placental location was determined by real-time ultrasonography.<sup>9</sup> The flow velocity waveforms were obtained with the mother lying comfortably in a slight lateral tilt according to a previously described method.<sup>9</sup> A 4 MHz continuous-wave Doppler device equipped with a real-time spectrum analyzer was used to obtain the uterine artery flow velocity waveforms. The systolic/diastolic ratio was used as an index of resistance in the vasculature distal to the point of insonation. The average of two measurements on each side was classified as right and left uterine artery flow velocity waveform, respectively. When necessary for comparisons, the mean of the right and left uterine arteries was classified as the mean uterine artery flow velocity waveform. In patients with unilateral placenta the uterine artery ipsilateral to the placenta was classified as placental uterine artery and the one contralateral to the placenta as nonplacental uterine artery.

For comparison with previous reports the entire sample ( $n = 123$ ) was analyzed according to the mean uterine artery flow velocity waveform without consideration of the placental location. Whenever we refer to placental and nonplacental uterine artery we consider only the patients with unilateral placentas ( $n = 67$ ), excluding the patients with central placentas.

The flow velocity waveforms were classified as abnormal if there was diastolic notching in early diastole or if the respective value of the systolic/diastolic ratio exceeded the 95th percentile of our normal values or both. In patients with unilateral placentas the established value is 2.3 for the placental and 3.7 for the nonplacental uterine artery. In patients with central placentas this value is 2.8 and represents the mean of the two uterine arteries.<sup>13</sup> The difference between the right and left uterine artery systolic/diastolic ratio was termed uterine artery discordance.

Statistical analysis was performed by  $\chi^2$  test for comparison of frequencies of various pregnancy outcomes. The relationship of placental, nonplacental, and mean uterine arteries was explored with Pearson's correlation coefficient. Comparisons of clinical and Doppler parameters between groups were performed by Student  $t$  test for independent samples with unequal variances.

## Results

Data from 123 patients were analyzed. Of those 123 patients, 67 had unilateral placentas and 56 had central placentas. There were no differences between the two groups in regard to gravidity, parity, degree of hypertension, degree of proteinuria, gestational age at delivery, and birth weight. However, the uterine artery discordance and the length of stay in the neonatal intensive care unit were different ( $p < 0.05$  and  $p = 0.05$ , respectively). There were seven perinatal deaths in this group of 123 patients with five (72%) occurring in patients with unilateral placentas (Table I). Comparison of patients according to abnormality in the three uterine vessel subgroups (normal vs abnormal mean uterine artery flow velocity waveform, normal vs abnormal placental uterine artery, and normal vs abnormal nonpla-

Antepartum test result*	Maternal mean arterial pressure (mm Hg)	Apgar score	Indication for delivery
Abnormal	84	1	Fetal distress
Abnormal	110	8	Fetal distress
Not done	123	0	Intrauterine fetal death
Normal	94	0	Intrauterine fetal death
Abnormal	120	9	Fetal distress
Normal	97	0	Intrauterine fetal death
Abnormal	110	8	Fetal distress

central uterine artery revealed no differences in the degree of proteinuria or hypertension.

Tables II through IV demonstrate comparisons of clinical outcomes between normal and abnormal uterine arteries. It is evident that an abnormal placental uterine artery is the best predictor of poor outcome, the abnormal mean uterine artery is second best, and the nonplacental uterine artery was the poorest predictor of clinical outcome. Eighty patients underwent delivery by cesarean section. The majority of them (82%) did so for fetal or maternal indications directly related to the hypertensive disorders and only 18% for obstetric indications not related to the patients' hypertensive disorder. This was the case in all groups of patients. Table V lists the indications for cesarean deliveries. All patients who delivered before 37 completed weeks ( $n = 62$ ) did so because of fetal or maternal indications related to the hypertensive disorder.

The presence of notching in the placental uterine artery regardless of systolic/diastolic value is associated with lower birth weight in neonates of similar gestational age at delivery ( $p < 0.02$ ). In comparing the degree of discordance between right and left uterine arteries in patients with notching and those without, we found that placental uterine artery notching does not affect the degree of discordance between the two uterine arteries in the two groups ( $p = 0.7$ ). However, the presence of notching in the nonplacental uterine artery is associated with a greater discordance between right and left uterine arteries ( $p < 0.0001$ ). Regression analysis of the degree of discordance (change in systolic/diastolic ratio) on the systolic/diastolic ratio of the placental and nonplacental uterine artery and mean uterine artery flow velocity waveform from all patients revealed no correlation between uterine artery discordance and placental uterine artery resistance ( $r = -0.09$ ,  $p = 0.5$ ). To the contrary, there exists a significant correlation between uterine artery discordance and nonplacental uterine artery resistance ( $r = 0.74$ ,  $p < 0.0001$ ). The mean resistance correlates also with the uterine artery discordance but to a lesser degree ( $r = 0.44$ ,  $p < 0.003$ ). Comparisons of clinical characteristics according to the degree of discordance

(change in systolic/diastolic = 1, 1.5, and 2) failed to disclose any statistically significant differences, except that the values of the mean uterine artery flow velocity waveform and nonplacental uterine artery were significantly higher in patients with higher discordance. This was true for the entire group and in the group with unilateral placenta. Uterine artery discordance became clinically discriminatory for poor pregnancy outcome only in association with an abnormal mean uterine artery flow velocity waveform.

Seventy-five percent of the patients with abnormal placental uterine artery also have abnormal mean uterine artery flow velocity waveform ( $p < 0.004$ ), and 81% of those with abnormal nonplacental uterine artery also have abnormal mean uterine artery flow velocity waveform ( $p < 0.0001$ ). Thirty percent of the patients with normal placental uterine artery have abnormal mean uterine artery flow velocity waveform ( $p < 0.004$ ), in contrast to only 4% of the patients with normal nonplacental uterine artery who have abnormal mean uterine artery flow velocity waveform ( $p < 0.0001$ ). Abnormal mean uterine artery flow velocity waveform correlates better with abnormal nonplacental uterine artery than with an abnormal placental uterine artery ( $r = 0.75$ ,  $p < 0.0001$  and  $r = 0.46$ ,  $p < 0.001$ , respectively).

#### Comment

This is the first report to evaluate the clinical significance of abnormal uterine artery resistance for each uterine artery separately in relation to placental location. Previous reports have examined the clinical significance of the subplacental arcuate artery,<sup>6</sup> either one of the two ascending uterine artery branches,<sup>14</sup> or the average of the two uterine arteries.<sup>5</sup> As expected, the results were variable. In part the differences are due to different methods used by various investigators and, to a significant extent, to the differences between the two uterine arteries.

Trudinger et al.<sup>6</sup> limited signal sampling only in the subplacental bed where one can only identify signals from radial and arcuate arteries. Either one of these vessels individually is responsible for only a limited portion of placental bed perfusion and as such it may very well be normal in the presence of significant placental pathology in parts of the placental bed perfused by other arcuate and radial arteries. An abnormal subplacental flow velocity waveform, however, is more likely to be associated with placental pathology because the bulk of blood volume that flows through the subplacental radial and arcuate arteries is directed toward the placental spiral arteries.

Campbell et al.<sup>14</sup> evaluated both ascending uterine arteries with pulsed-wave Doppler and used the most abnormal vessel (highest resistance). From their description and technique it is very likely that some times

**Table II.** Comparison of clinical outcomes in patients with normal versus abnormal mean uterine artery resistance

Clinical outcomes	Mean uterine artery status				Significance
	Abnormal (n = 79, 100%)		Normal (n = 44, 100%)		
Small for gestational age	28	(35%)	8	(18%)	NS
5 min Apgar score <7	7	(9%)	1	(2%)	NS
Preterm delivery	52	(66%)	10	(23%)	$p < 0.001$
Cesarean delivery	58	(73%)	22	(50%)	$p < 0.02$
Perinatal deaths	6	(7.6%)	1	(2%)	NS
Newborn intensive care unit stay	24	(30%)	1	(2%)	$p < 0.001$
Patients with proteinuria	35	(44%)	17	(39%)	NS

NS, Not significant.

**Table III.** Comparison of clinical outcomes in patients with normal versus abnormal placental uterine artery resistance

Clinical outcomes	Placental uterine artery status				Significance
	Abnormal, (n = 40, 100%)		Normal (n = 27, 100%)		
Small for gestational age	17	(43%)	3	(11%)	$p < 0.03$
5 min Apgar score <7	4	(10%)	2	(7%)	NS
Preterm delivery	26	(65%)	9	(33%)	$p < 0.03$
Cesarean delivery	33	(83%)	16	(60%)	$p < 0.05$
Perinatal deaths	4	(10%)	1	(3.7%)	NS
Neonatal intensive care unit stay	11	(28%)	4	(15%)	$p < 0.001$
Patients with proteinuria	17	(42%)	17	(62%)	NS

NS, Not significant.

they obtained placental and other times nonplacental uterine artery signals. By this method they achieved good sensitivity in predicting problem pregnancies remote from term (18 to 20 weeks' gestation), although the positive predictive value of an abnormal outcome was low. Steel et al.<sup>7</sup> examined one of the two uterine arteries without prior knowledge of the placental location to screen patients at risk for preeclampsia. Abnormal uterine artery resistance at 24 weeks' gestation identified correctly 63% of the patients who subsequently developed preeclampsia. McParland et al.<sup>15</sup> in a subsequent study, treated patients who had abnormal uterine artery resistance with 75 mg aspirin every day in a random, double-blind fashion. The group of patients who were treated presented with a lower incidence of pregnancy-induced hypertension, proteinuric preeclampsia, and intrauterine growth retardation.

Our data suggest that an abnormal placental uterine artery is the best predictor of poor pregnancy outcome, whereas the average of both uterine arteries is the next best and the nonplacental is the least. Several previous reports have clearly demonstrated that the placental uterine artery has a significantly lower resistance than the nonplacental uterine artery.<sup>8, 16, 17</sup> Therefore, when the placental uterine artery is abnormal, there must be a significant degree of placental abnormality. In addition

it should be kept in mind that the placental uterine artery reflects pathologic conditions of the majority of the placental bed vasculature. On the other hand, the nonplacental uterine artery is perfusing primarily nonplacental myometrial vessels to the extent that the placenta is unilaterally located.

It seems that in a group of patients with hypertensive disorders and similar risks for poor outcome the presence of a unilateral placenta increases the risk for perinatal death. Seventy-two percent of perinatal deaths occurred in the group with unilateral placentas and only 28% in the group with centrally located placentas. A unilateral placenta was also found to be associated with longer stay in the newborn intensive care unit and increased degree of discordance between the two uterine arteries. Schulman et al.<sup>8</sup> reported significantly increased risk for poor pregnancy outcome with increasing uterine artery discordance. They also found a significant degree of correlation between mean uterine artery flow velocity waveform systolic/diastolic ratio and change in systolic/diastolic ratio (left - right uterine artery systolic/diastolic ratio). Our findings are partially in agreement with regard to poor pregnancy outcome. However, our data demonstrate a moderate degree of correlation between mean uterine artery flow velocity waveform systolic/diastolic ratio and change in

**Table IV.** Comparison of clinical outcomes in patients with normal versus abnormal nonplacental uterine artery resistance

Clinical outcomes	Nonplacental uterine artery status				Significance
	Abnormal (n = 47, 100%)		Normal (n = 20, 100%)		
Small for gestational age	17	(36%)	3	(15%)	NS
5 min Apgar score	4	(9%)	2	(10%)	NS
Preterm delivery	30	(64%)	5	(25%)	<i>p</i> < 0.04
Cesarean delivery	37	(79%)	12	(60%)	NS
Perinatal deaths	4	(8.5%)	1	(5%)	NS
Neonatal intensive care unit stay	15	(32%)	2	(10%)	NS
Patients with proteinuria	22	(46%)	11	(55%)	NS

NS, Not significant.

**Table V.** Indications for cesarean section and number of patients in each category

Indication	No. of patients	Proportion of total (n = 123) (%)
Fetal distress	30*	24
Severe preeclampsia	36*	29
Repeat cesarean section	5	4
Diabetes mellitus	4	3
Cephalopelvic disproportion	4	3
Genital herpes	1	1
TOTAL	80	65

\*Sixty-two of these 66 patients were delivered before 37 completed weeks' gestation.

systolic/diastolic ratio. In contrast, there exists a significant degree of correlation between the nonplacental uterine artery systolic/diastolic ratio and the change in systolic/diastolic ratio. The difference may be due to different methodology. Schulman et al.<sup>8</sup> considered as abnormal a systolic/diastolic ratio of  $\geq 2.8$  for both placental and nonplacental uterine arteries. We do not concur with this method, since the 95th percentile of the systolic/diastolic ratio for the placental uterine artery is 2.3 and for the nonplacental uterine artery is 3.7 in our normal population.<sup>12</sup> Our data suggest that the degree of abnormality of the mean uterine artery flow velocity waveform is strongly influenced by the nonplacental uterine artery in patients with unilateral placenta and thus may lose some of its sensitivity because the nonplacental uterine artery may be abnormal in the absence of significant placental pathology.

We conclude that in patients with hypertension, placental uterine artery resistance is a better predictor of poor outcome than the mean and the nonplacental uterine artery. In the same patients the presence of a unilateral placenta is a significant risk factor associated with increased perinatal morbidity and mortality. To extract the best information from uterine artery flow velocity waveform analysis, it is important that the pla-

cental location is known and each uterine artery is evaluated individually. For this purpose appropriate reference values that account for placental location should be used. Increasing use of ultrasonographic equipment with Doppler capabilities will render this more feasible and thus improve the level of information about the uteroplacental vasculature in patients with hypertensive disorders.

**REFERENCES**

1. Khong TY, DeWolf F, Robertson WB, Brosens I. Inadequate maternal vasculature response to placentation in pregnancies complicated by pre-eclampsia and by small for gestational age infants. *Br J Obstet Gynaecol* 1986;93:1049-59.
2. Steel SA, Pearce M, Chamberlain GV. Doppler ultrasound of the uteroplacental circulation as a screening test for severe preeclampsia with intra-uterine growth retardation. *Eur J Obstet Gynecol* 1988;28:279-87.
3. Fleischer A, Schulman H, Farmakides G, et al. Uterine artery doppler velocimetry in pregnant women with hypertension. *AM J OBSTET GYNECOL* 1986;154:806-13.
4. Schulman H. The clinical implications of Doppler ultrasound analysis of the uterine and umbilical arteries. *AM J OBSTET GYNECOL* 1987;156:889-93.
5. Schulman H, Fleischer A, Farmakides G, Bracero L, Rochelson B, Grunfeld L. Development of uterine artery compliance in pregnancy as detected by Doppler ultrasound. *AM J OBSTET GYNECOL* 1986;155:1031-6.
6. Trudinger BJ, Giles WB, Cook CM. Uteroplacental blood flow velocity-time waveforms in normal and complicated pregnancy. *Br J Obstet Gynaecol* 1985;92:39-45.
7. Steel SA, Pearce JM, McParland P, et al. Early Doppler ultrasound screening in prediction of hypertensive disorders of pregnancy. *Lancet* 1990;335:1548-51.
8. Schulman H, Ducey J, Farmakides G, et al. Uterine artery Doppler velocimetry: the significance of divergent systolic/diastolic ratios. *AM J OBSTET GYNECOL* 1987;157:1539-42.
9. Kofinas AD, Penry M, Greiss FC, Meis PJ, Nelson LH. The effect of placental location on uterine artery flow velocity waveforms. *AM J OBSTET GYNECOL* 1988;159:1504-8.
10. Kofinas AD, Penry M, Swain M, Hatjis CG. Effect of placental laterality on uterine artery resistance and development of preeclampsia and intrauterine growth retardation. *AM J OBSTET GYNECOL* 1989;161:1536-9.
11. American College of Obstetricians and Gynecologists. Management of preeclampsia. Washington: American College of Obstetricians and Gynecologists, 1986; ACOG technical bulletin no 91.

12. Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. *AM J OBSTET GYNECOL* 1976;126:555-62.
13. Kofinas AD, Espeland MA, Penry M, Swain M, Hatjis CG. Uteroplacental Doppler flow velocity waveform indices in normal pregnancy: a statistical exercise and the development of appropriate reference values. *Am J Perinatol* [In press].
14. Campbell S, Pearce MF, Hackett G, Cohen-Overbeek T, Hernandez C. Qualitative assessment of uteroplacental blood flow: early screening test for high-risk pregnancies. *Obstet Gynecol* 1986;68:649-53.
15. McParland P, Pearce JM, Chamberlain CVP. Doppler ultrasound and aspirin in recognition and prevention of pregnancy-induced hypertension. *Lancet* 1990;335:1552-5.
16. Chambers SE, Johnstone FD, Muir BB, Hoskins P, Haddad NG, McDicken WN. The effects of placental site on the arcuate artery flow velocity waveform. *J Ultrasound Med* 1988;7:671-3.
17. Campbell S, Bewles S, Cohen-Overbeek T. Investigation of the uteroplacental circulation by Doppler ultrasound. *Semin Perinatol* 1987;6:362-8.