Ultrasound Obstet Gynecol 2004; **23**: 46–49
Published online 7 November 2003 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.908

Effect of parity on second-trimester uterine artery Doppler flow velocity and waveforms

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KEYWORDS: Doppler; second-trimester; parity; uterine arteries

ABSTRACT

Objectives *To investigate the relationship between second-trimester uterine artery Doppler findings and parity in a large pregnant population.*

Methods *Uterine artery Doppler studies were performed in all singleton pregnancies at 18–23 weeks of gestation. The mean uterine artery resistance index and the presence or absence of protodiastolic notches were recorded. Two groups were identified: pregnancies not complicated by pre-eclampsia, and pregnancies with pre-eclampsia severe enough to require delivery at or before 32 weeks of gestation.*

Results *In the 4132 pregnancies uncomplicated by pre-eclampsia, parity was shown to be an independent predictor for both mean uterine artery resistance index (beta = 0.073,* $P < 0.001$*) and the presence of bilateral protodiastolic notches (odds ratio = 0.67; 95% CI, 0.45–0.98). In the 17 pregnancies complicated with severe pre-eclampsia, uterine artery Doppler indices showed a trend towards being better predictors of disease in nulliparous compared with parous women.*

Conclusion *Parity has a significant effect on the resistance index and the prevalence of protodiastolic notching in the uterine artery flow waveforms. This difference is clinically noticeable in its effect on notching. These findings suggest that some permanent modification may persist in the maternal vessels after a successful pregnancy, altering their impedance in subsequent pregnancies. Copyright © 2003 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Ultrasound assessment of uterine artery resistance in pregnancy has been used to screen for the subsequent development of pre-eclampsia. Although numerous studies have demonstrated the value of second-trimester uterine artery Doppler screening of high-risk populations, its role in low-risk populations is still far from defined[1–7]. The conflicting findings of these publications may be explained by variation in recruitment, methodology and definition of outcomes between the studies.

Nulliparity is a well known risk factor for pre-eclampsia[8] and parity may have an effect on uterine artery blood flow in consecutive pregnancies. The aim of the current study was to investigate the relationship between second-trimester uterine artery Doppler indices and parity in a large series of pregnancies not complicated by pre-eclampsia.

METHODS

All pregnancies booked and delivered at our hospital between September 1999 and December 2001 were identified from our computerized clinical database. We included in our study all singleton live births which had received ultrasound assessment of the uterine arteries between 18 and 23 weeks of gestation. Gestational age was calculated from the last menstrual period and confirmed by first-trimester ultrasound. All cases with chromosomal or structural abnormalities were excluded.

We identified pregnancies not complicated by pre-eclampsia and pregnancies in which severe pre-eclampsia developed. Pre-eclampsia was defined as blood pressure $> 140/90$ mmHg, and proteinuria ≥ 300 mg in 24 h, or two readings of at least 1+ on dipstick analysis of midstream or catheter urine specimens if no 24-h urine collection was available. Pre-eclampsia was defined as severe when delivery at or before 32 weeks of gestation was necessary for maternal or fetal indications.

At ultrasound examination, the right and left uterine arteries were identified at the apparent crossover with

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Accepted: 17 July 2003

the external iliac artery using color Doppler. Pulsed-wave Doppler was used to obtain uterine artery waveforms. When three similar consecutive waveforms were obtained, the presence of a protodiastolic notch was recorded, the resistance index (RI) measured, and the mean RI of the two vessels calculated[9]. The parity and smoking status of the mother were also recorded. All pregnancy outcomes were obtained from the delivery suite database.

Uterine artery RI required logarithmic transformation to give a better fit to the normal distribution. Therefore, standard deviations for RI are presented in terms of estimated coefficients of variation, i.e. as a proportion of the mean value rather than as an absolute value[10]. For inter-group comparisons, Student's *t*-test, the Mann-Whitney *U*-test, the χ^2 test or Fisher's exact test were used as appropriate. Multiple regression analysis was performed to investigate the relationship between parity and uterine artery RI values. Correlation matrix, collinearity and residual analysis were performed to verify the validity of the model. Logistic regression analysis was performed to investigate the relationship between parity and the absence or presence of protodiastolic uterine artery notches. Correlation matrix and residual analysis were performed to verify the validity of the model. All calculations were performed using the SPSS software package (release 10.0.5, SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 4132 singleton pregnancies not complicated by pre-eclampsia were identified. Of them, 3091 (74.8%) were nulliparous and 1041 (25.2%) parous. Demographic characteristics and uterine artery Doppler measurements of the whole study population and in the two groups are shown in Table 1. A multiple regression model including maternal age, smoking status, gestational age at scan and parity as independent variables with mean RI as the dependent variable was calculated (Table 2, adjusted $R^2 = 0.008$, $P < 0.001$). A logistic regression model including maternal age, smoking status, gestational age at scan and parity as independent variables was calculated to predict the presence of bilateral uterine artery notches (Table 3, $R^2 = 0.035$, $P < 0.005$). In both these models, parity was shown to be significantly associated with variation in uterine artery RI and the prevalence of notches.

During the study period, severe pre-eclampsia was observed in 17 cases. Thirteen (76%) of these patients were nulliparous, and 4 (24%) parous. There was a trend for higher RI values in nulliparous women, but this did not reach statistical significance (Figure 1, $P = 0.16$). The distribution of uterine artery notches in the cases with severe pre-eclampsia is displayed in Table 4. Despite a trend for a higher prevalence of notches in nulliparous women, the difference did not reach statistical significance ($P = 0.44$).

Table 2 Results of a multiple regression model with mean resistance index (RI) as the dependent variable (adjusted $R^2 = 0.008$, $P < 0.001$) in 4132 pregnancies not complicated by pre-eclampsia

Independent variable	*Beta**	P
Maternal age	0.020	0.214
Smoking	0.006	0.687
GA at scan	−0.050	0.001
Parity ≥ 1	0.073	< 0.001

Uterine artery mean RI required logarithmic transformation.
*Standardized regression coefficient. GA, gestational age.

Table 3 Results of a logistic regression model to predict the presence of bilateral uterine artery protodiastolic notches in 4132 pregnancies not complicated by pre-eclampsia

Independent variable	*Odds ratio**	*95% CI*	P
Maternal age	1.04	1.01–1.06	< 0.01
Smoking	1.13	0.75–1.68	0.56
GA at scan	1.03	0.88–1.22	0.68
Parity ≥ 1	0.67	0.45–0.98	0.04

GA, gestational age.

Table 1 Demographic characteristics and uterine artery Doppler measurements of 4132 women with pregnancy not complicated by pre-eclampsia

	Total (n = 4132)	*Nulliparous (n = 3091)*	*Parous (n = 1041)*	P
Maternal age (years, mean ± SD)	29.4 ± 5.9	28.6 ± 5.8	31.6 ± 5.4	< 0.001†
Smokers (%)	13.9	12.0	19.6	< 0.001‡
GA at scan (weeks, mean ± SD)	21.1 ± 0.9	21.1 ± 0.9	21.2 ± 0.9	0.003†
GA at delivery (weeks, mean ± SD)	39.5 ± 2.2	39.7 ± 2.2	39.2 ± 2.3	< 0.001†
RI (mean (%))*	0.54 (17)	0.54 (17)	0.56 (18)	< 0.001†
Notches (*n* (%))				< 0.001‡
0	3498 (84.7)	2578 (83.4)	920 (88.4)	
1	435 (10.5)	348 (11.3)	87 (8.4)	
2	199 (4.8)	165 (5.3)	24 (2.3)	

*Since a logarithmic transformation was used for the mean resistance index, the SD is expressed as a percentage of magnitude; †Student's *t*-test; ‡chi-square test; GA, gestational age; RI, resistance index.

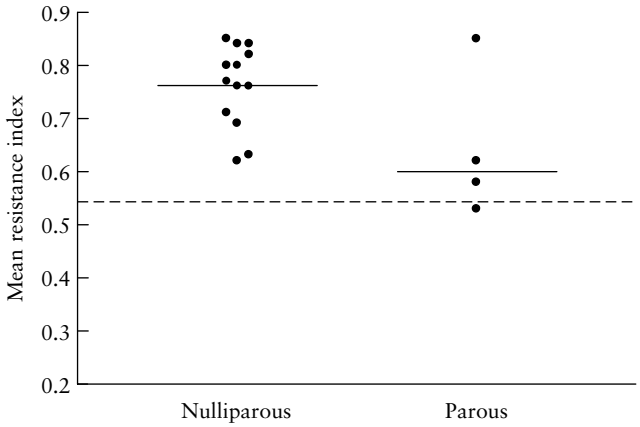

Figure 1 Distribution of mean uterine artery resistance index (RI) values in nulliparous ($n = 13$) and parous ($n = 4$) women with pregnancies complicated by severe pre-eclampsia. Horizontal lines indicate means. The dashed line indicates the mean RI in pregnancies not complicated by pre-eclampsia ($n = 4132$).

Table 4 Distribution of uterine artery protodiastolic notches in nulliparous and parous women with pregnancies complicated by severe pre-eclampsia ($n = 17$)

	Nulliparous (n = *13*)	*Parous* (n = *4*)
Notches (*n* (%))		
0	2 (15)	2 (50)
1	1 (8)	1 (25)
2	10 (77)	1 (25)

DISCUSSION

The findings of this study indicate that parity has a significant effect on uterine artery Doppler indices measured in the second trimester of pregnancy. Although parity affects both uterine artery RI and the prevalence of notches, the effect on the latter is likely to be of greater clinical significance. In our series of uncomplicated pregnancies, parous women presented with slightly higher RI values when compared with nulliparous women. Although this difference was statistically significant, the multiple regression model using parity, maternal age, gestational age at ultrasound scan and smoking status was only able to explain less than 1% of the variance in mean uterine artery RI. Additionally, the difference in mean RI between nulliparae and multiparae was smaller than the established interobserver variability of uterine artery Doppler[11,12].

In contrast, the prevalence of protodiastolic notches was significantly lower in parous women. After correcting for confounding factors in the logistic regression model, the odds ratio for bilateral notches in parous women was 0.67 (95% CI, 0.45–0.98). Hence, nulliparous women are 50% more likely to have bilateral notches than are parous women. These observations are supported by the findings described by Hafner *et al.*[13] who examined uterine artery perfusion in the first and second pregnancy in 1102 women. These authors observed that uterine pulsatility index (PI) in the same woman was similar in the first and second pregnancies, while notching appeared much more frequently in the first pregnancy.

Ideally the effect of parity should be demonstrated by comparing screening efficiency in nulliparous and parous women. However, a policy of two-stage screening[2] with aspirin administration was followed in screen-positive pregnancies. This management policy, which is expected to decrease the risk of developing pre-eclampsia in the treated pregnancies, may have affected the two sub-groups to different extents[14]. Therefore, it is not appropriate to draw any conclusions from our data regarding the incidence of pre-eclampsia and the sensitivity, specificity or positive and negative predictive values of the test in the two groups. However, it is relevant to emphasize that almost 80% of nulliparae with pre-eclampsia severe enough to require delivery at 32 weeks or earlier presented with bilateral uterine notches, which were observed in only 25% of parous women with a similar disease severity. We are aware of the limits imposed by the small number of cases and the lack of statistical significance of this difference, but these findings suggest that the sensitivity of the test for the most severe cases is higher in the first pregnancy.

It is important to note that parity paradoxically served to increase the mean uterine artery RI and decrease the prevalence of notching. The literature is of little help in understanding why a previous pregnancy should have such contrasting effects on uterine artery Doppler indices and notching. The RI and PI are popular parameters used for characterizing arterial waveforms at Doppler ultrasound. Although their physiological meaning is still under dispute, mathematical models, *in-vitro* experiments and data from sheep all suggest that PI and RI are affected by both downstream resistance and vessel compliance[15–19]. However, clinically PI and RI are more directly dependent on factors affecting downstream vascular resistance, such as intervillous obstruction and failed spiral artery invasion[15,17,18], whereas uterine artery notching may be an effect of abnormal compliance of the uterine/arcuate arteries[15].

The findings of this study must be explained by the effect of pregnancy on the maternal vasculature. During placentation, trophoblastic cells infiltrate the spiral arteries. As a result, the thick-walled and muscular spiral arteries are transformed into thin-walled and floppy vessels that can dilate and accomodate the increased uteroplacental blood flow necessary for a successful pregnancy[20,21]. It is possible that some permanent modification persists in the maternal vessels as an effect of this process, altering their compliance in subsequent pregnancies. These changes may explain the lower prevalence of notches in parous women. Further studies are needed to investigate this physiological hypothesis and its effect on uterine artery Doppler screening programs.

ACKNOWLEDGMENT

Dr. Prefumo was supported by a Marie Curie Fellowship of the European Community programme Quality of Life under contract number QLGA-CT-2000-52145.

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