

## ORIGINAL ARTICLE

# Umbilical artery Doppler at 19 to 22 weeks of gestation in the prediction of adverse pregnancy outcomes

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## ABSTRACT

**Objective** The aim of this study was to determine the clinical utility of Doppler assessment of the umbilical artery in the second trimester scan for predicting adverse pregnancy outcomes.

**Methods** Singleton pregnancies that had undergone routine anomaly scan at 19 to 22 weeks of gestation with umbilical and uterine artery Doppler measurements. Receiver operating characteristic curves were constructed to evaluate the ability of umbilical artery pulsatility index (PI) to predict small for gestational age and preeclampsia.

**Results** The final study population comprised 4565 singleton pregnancies. Multiple regression analysis showed significant independent contribution of umbilical artery PI in predicting SGA <10th and SGA <5th centiles (adjusted odds ratios of 2.51 and 3.51, respectively). By using a cutoff of umbilical artery PI >90th centile, the likelihood ratio of SGA <5th centile is 2.3 (95% CI: 1.7–3.0).

**Conclusions** Umbilical artery PI at 19 to 22 weeks of gestation is significantly associated with SGA below the tenth and fifth centiles. A multivariate model combining umbilical and uterine artery Doppler measurements with additional maternal and sonographic characteristics may help predict small for gestational age, particularly those below the fifth centile. © 2014 John Wiley & Sons, Ltd.

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## INTRODUCTION

Over the past two decades, several studies have shown that pregnancies failing to establish low-resistance circulation during placental development are at a substantial risk of adverse pregnancy outcomes, such as preeclampsia, small for gestational age (SGA), placental abruption, and intrauterine death.<sup>1</sup> Second trimester assessment of uteroplacental circulation by Doppler ultrasound has been proposed as a screening tool in the prediction of adverse pregnancy outcomes of conditions related to abnormal placentation and inadequate uteroplacental blood flow, such as preeclampsia and fetal growth restriction,<sup>2,3</sup> particularly among high-risk women.<sup>4</sup>

Doppler velocimetry of the umbilical artery also provides a noninvasive measure of the fetoplacental hemodynamic state, and their indices indirectly reflect impedance of downstream circulation. This is supported by the significant association between abnormal Doppler indices and fetal hypoxia, fetal acidosis, and adverse perinatal outcomes.<sup>5</sup> Although, umbilical artery has been showed to be a valuable predictor of adverse perinatal outcomes in established preeclampsia and fetal growth restriction,<sup>6</sup> there are limited data exploring the association of abnormal umbilical artery Doppler in low-risk patients during the

routine second trimester scan and adverse pregnancy outcomes. We identified one previous study reporting increased pulsatility index (PI) in the umbilical artery at 12 to 16 weeks and subsequent development of preeclampsia and SGA infants in a non-selected population.<sup>7</sup> Recently, a Cochrane's review identified five trials carried out in the 1990s studying umbilical artery and uterine artery in low-risk populations.<sup>8</sup> It was reported that there is no conclusive evidence that the routine use of umbilical or uterine artery benefit mother or fetus for screening of adverse pregnancy outcomes. However, four of these studies were carried after 26 weeks of gestation, and only one was carried out at 19 to 22 weeks of gestation with an additional scan at 32 weeks.

Herein, we aim to explore the association of umbilical artery PI in the routine second trimester scan with subsequent adverse pregnancy outcomes.

## MATERIAL AND METHODS

### Study population and clinical measurements

The study included pregnant women undergoing routine anomaly scan at 19 to 22 weeks of gestation at the 'Virgen de la Arrixaca' Clinic University Hospital (Murcia, Spain) between

August 2011 and August 2012. We searched our computer database (ViewPoint, Webling, Germany) to obtain maternal obstetric characteristics, such as ethnicity, age, weight, parity, cigarette smoking, and medical history including hypertension and diabetes mellitus. All pregnancies were singleton and dated according to last menstrual period or crown-rump length as appropriate. Outcomes were recorded from labor ward and hospital notes. Exclusion criteria included major fetal malformations, aneuploidy, spontaneous fetal loss at 19 to 22 weeks, and termination of pregnancy. Outcomes were SGA at delivery, which was classified according to birth weight below the tenth and fifth centiles for gestational age<sup>9</sup> and preeclampsia. Preeclampsia was diagnosed on the basis of the criteria stated by the International Society for the Study of Hypertension in Pregnancy.<sup>10</sup>

### Doppler examination

Routine anomaly and Doppler ultrasound examinations were performed by obstetricians with more than 5 years of experience and certified by the Fetal Medicine Foundation of London ([www.fetalmedicine.com](http://www.fetalmedicine.com)) using ultrasound equipment (Voluson 730 Expert, GE Medical Systems, Austria). PI of each uterine artery was measured by transabdominal ultrasound as previously described,<sup>11</sup> and the mean of these two values was used for further analysis. Similarly, a free-floating loop of the fetal cord was identified to individualize the umbilical artery by color-flow mapping. The sampling gate was set at 2 mm to cover the whole vessel. Care was taken to ensure that the angle of insonation was less than 60°. PI was measured at least in three consecutive waveforms. At our hospital, Doppler examinations of both umbilical and uterine arteries are routinely recorded during the second trimester scan.

To determine the screening efficiency of umbilical artery PI and uterine artery mean PI for predicting adverse outcomes, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios. Additionally, multivariate analysis was performed to determine the significant independent contribution of umbilical artery PI and uterine artery mean PI for predicting adverse outcomes adjusted for maternal weight and cigarette smoking, and the results are presented as adjusted odds ratios. Additionally, we constructed a receiver operating characteristic curve to show the detection rate of SGA below the fifth centile and false positive rates for different cutoffs of uterine artery mean PI, and umbilical artery PI and a multivariate model combining uterine and umbilical artery with maternal weight and smoking. All calculations were performed using SPSS v10 (SPSS Inc., Chicago, IL, USA). A *p* value of <0.05 was considered statistically significant.

We have adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines on reporting.<sup>12</sup>

### RESULTS

A total of 5109 women underwent routine anomaly ultrasound scan at 19 to 22 weeks of gestation. We excluded 544 (10.6%) women due to missing outcome data (*n*=487), major fetal defect or abnormal karyotype (*n*=35), spontaneous fetal loss detected in the anomaly scan or termination of pregnancy for other reasons (*n*=22). A total of 4565 pregnancies underwent

further analysis. The number of SGA infants below the tenth centile was 518 (11.3%) and below the fifth centile was 279 (6.1%). The prevalence of women with preeclampsia was 1.2%, which is consistent with a previous study on the prevalence of preeclampsia in Spain.<sup>13</sup> The demographic details and obstetric outcomes of the population study are shown in Table 1.

The 90th and 95th centiles for umbilical artery PI were 1.48 and 1.56, respectively. Similarly, the 90th and 95th centiles for uterine artery mean PI were 1.39 and 1.54, respectively. Multiple regression analysis showed significant independent contribution in predicting SGA <10th centile and SGA <5th centile by umbilical artery PI, uterine artery mean PI, maternal weight and smoking status. However, preeclampsia was only predicted by uterine artery mean PI and maternal weight (Table 2).

The performance of the screening test for different cutoffs of umbilical and uterine artery PIs are shown in Table 3. The essential findings are that uterine artery PI >95th or 90th centiles perform well for predicting preeclampsia. Umbilical artery PI has poor screening characteristics for predicting preeclampsia. Although SGA is better predicted by uterine artery PI than umbilical artery PI, the latter may add extra information in the prediction of SGA when considering PI

Table 1 Demographic and obstetric characteristics of the study population

Maternal age in years, median (IQR)	32 (28–35)
Maternal weight in kg, median (IQR)	64 (57.5–72)
Ethnicity, n (%)	
Caucasian	4507 (98.7)
Black	40 (0.9)
Other	18 (0.4)
Smoking, n (%)	723 (15.8)
Nulliparous, n (%)	2785 (61)
Conception, n (%)	
Spontaneous	4374 (95.8)
<i>In vitro</i> fertilization	167 (3.7)
Other	24 (0.6)
Medical history, n (%)	
Hypertension	25 (0.5)
Diabetes mellitus	31 (0.7)
History of preeclampsia	7 (0.2)
Ultrasound gestational age in weeks, median (IQR)	20.5 (20–21)
Uterine artery mean PI, median (IQR)	0.97 (0.8–1.16)
Umbilical artery PI, median (IQR)	1.2 (1.10–1.33)
Obstetric outcome	
Birth weight in g, median (IQR)	3280 (2950–3580)
Intrauterine death, n (%)	37 (0.8)
Placental abruption, n (%)	9 (0.2)
Preeclampsia, n (%)	56 (1.2)
SGA <10th centile, n (%)	518 (11.3)
SGA <5th centile, n (%)	279 (6.1)

IQR, interquartile range; PI, pulsatility index; SGA, small for gestational age.

Table 2 Multiple regression analysis for predicting small for gestational age

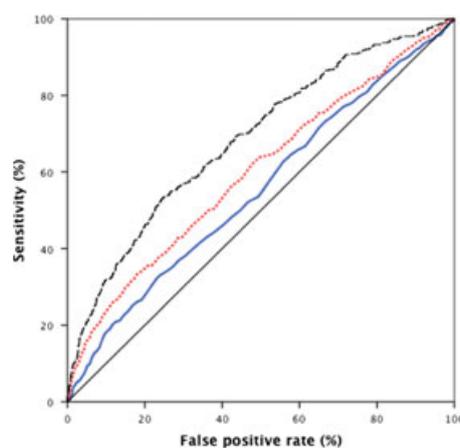
Variable	SGA <5th centile	SGA <10th centile	Preeclampsia
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Umbilical artery PI	3.51 (1.74–7.09)*	2.51 (1.46–4.31)*	1.07 (0.24–4.67)
Mean uterine artery PI	4.85 (3.19–7.39)*	4.31 (3.09–6.01)*	6.27 (3.02–13.01)*
Maternal weight, kg	0.96 (0.95–0.97)*	0.97 (0.96–0.98)*	1.03 (1.02–1.05)*
Smoking	2.70 (1.99–3.66)*	2.44 (1.92–3.12)*	0.43 (0.15–1.21)

OR, adjusted odds ratio; PI, pulsatility index.  
\*p < 0.0001

Table 3 Performance of different cutoffs of umbilical and uterine artery pulsatility indices for predicting adverse outcomes

	Sensitivity	Specificity	PPV	NPV	FPR	LR (95% CI)
Preeclampsia						
Uterine artery PI > p95	21.20	95.2	5.7	98.9	4.8	6.0 (3.6–10.2)
Uterine artery PI > p90	32.7	90.7	4.6	99	9.3	4.8 (3.3–6.8)
Umbilical artery PI > p95	7.8	95.2	2	98.8	4.8	1.7 (0.7–4.4)
Umbilical artery PI > p90	11.8	90.3	1.5	98.8	9.7	1.2 (0.6–2.6)
SGA < 10th centile						
Uterine artery PI > p95	13.80	96.1	31.1	89.8	3.9	3.9 (3.0–5.3)
Uterine artery PI > p90	21.2	91.9	24.8	90.2	8.1	3.1 (2.5–3.8)
Umbilical artery PI > p95	7.3	95.2	16.9	89.2	4.8	1.7 (1.2–2.4)
Umbilical artery PI > p90	15.8	91.1	18	89.7	8.9	1.9 (1.5–2.4)
SGA < 5th centile						
Uterine artery PI > p95	16.50	95.7	19.7	94.6	4.3	4.3 (3.1–6.0)
Uterine artery PI > p90	24.2	91.4	15.4	94.9	8.6	3.4 (2.7–4.3)
Umbilical artery PI > p95	8.9	95.4	10.9	94.3	4.6	2.0 (1.3–3.1)
Umbilical artery PI > p90	18.6	90.9	11.4	94.7	9.1	2.3 (1.7–3.0)

FPR, false positive rate, LR, likelihood ratio; NPV, negative predictive value; PI, pulsatility index; PPV, positive predictive value.



		AUC (95%CI)	p value
—	Umbilical artery PI	0.55 (0.52-0.58)	<.05
.....	Uterine artery, mean PI	0.60 (0.57-0.63)	<.05
-----	Logistic regression model	0.69 (0.66-0.71)	<.05

Figure 1 Receiver operating characteristics curves for umbilical artery pulsatility index (PI), mean uterine artery PI, and a logistic regression model based on the combination of both maternal weight and smoking status for predicting small for gestational age below the fifth centile

>90th centile as shown in Table 3 by using its likelihood ratio (2.3, 95% CI: 1.7–3.0).

Receiver operating characteristic curve analysis shows that a multivariate model combining Doppler and maternal characteristics perform best for predicting SGA <5th centile (area under curve: 0.69,  $p < 0.05$ ) (Figure 1).

## DISCUSSION

To our knowledge, this is the first study in a non-selected population reporting a significant association between high umbilical artery PI in the routine second trimester scan and the subsequent development of SGA infants. Umbilical artery Doppler is normally used to monitor SGA fetuses and those with abnormal umbilical blood flow are considered a subgroup at a higher risk of adverse perinatal outcomes<sup>14</sup> including increased mortality and morbidity rates related to fetal hypoxia and acidosis.<sup>15,16</sup> This management is supported by the hypothesis that fetal growth restriction develops after severe villous vasoconstriction.<sup>17</sup> In most of fetuses with growth restriction, Doppler blood flow in the uterine arteries is also abnormal, which also suggests that uteroplacental blood flow is reduced.<sup>18</sup>

In our study, preeclampsia or SGA was best predicted by higher uterine artery PI at mid-gestation, which is consistent with previous studies.<sup>3,19,20</sup>

Although a recent study has shown a weak association between second trimester umbilical PI and subsequent preeclampsia, our data do not support such association.<sup>21</sup> The reasons for this discrepancy are unknown, but we can argue that the design study and preeclampsia prevalence rate are different between these two

studies. Thus, an additional prospective study might be useful in determining any association between umbilical artery Doppler and subsequent preeclampsia in women at low-risk.

Consistent with a recent report, we found a significant association between umbilical artery Doppler and SGA infant below the fifth and tenth centiles.<sup>21</sup> Because measurement of umbilical artery PI is a straightforward procedure during the routine second trimester scan, we believe that its introduction in clinical practice might improve the current detection rates of SGA infants.

We acknowledge some limitations of our study, such as the retrospective design and failure to distinguish between mild and severe preeclampsia. However, our findings are the basis for further prospective studies taking into account the valuable information provided by the measurement of umbilical artery PI in the second trimester scan for predicting adverse pregnancy outcomes. Additionally, here we confirm that Doppler examination of the uterine artery in the second trimester of pregnancy predicts preeclampsia and SGA.

### WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Umbilical artery Doppler is useful in the management of high-risk patients.

### WHAT DOES THIS STUDY ADD?

- Umbilical artery Doppler in the routine second trimester scan can predict small for gestational age infants.

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