

Uterine artery Doppler evaluation in twin pregnancies at 11 + 0 to 13 + 6 weeks of gestation

G. RIZZO*†, M. E. PIETROLUCCI*†, E. AIELLO†, A. CAPPONI‡ and D. ARDUINI†

*Fetal Medicine Center, Rome, Italy; †Department of Obstetrics and Gynecology, Università di Roma 'Tor Vergata', Rome, Italy;

‡Department of Obstetrics and Gynecology, Ospedale G.B. Grassi, Rome, Italy

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ABSTRACT

Objectives To compare uterine artery pulsatility index (PI) obtained at 11 + 0 to 13 + 6 weeks of gestation in singleton and twin pregnancies and to evaluate changes in PI values of twin pregnancies developing pre-eclampsia (PE) or small-for-gestational age (SGA) of either one or both fetuses.

Methods Uterine artery PI was measured in 421 twin pregnancies (384 dichorionic and 37 monochorionic) and in 500 singleton pregnancies. The measured mean and lowest uterine artery PI values were converted to multiples of the expected normal median (MoM) after correction for maternal body mass index, ethnicity and gestational age. The median PI-MoM values of twins were compared with those of singleton pregnancies. In twin pregnancies, PI-MoM values were analyzed according to chorionicity, development of early-onset (< 34 weeks) or late-onset (\geq 34 weeks) PE and SGA of one or both twins.

Results Uterine artery PI-MoM was significantly lower in twin compared with singleton pregnancies (mean $K = 174.31$, $P < 0.0001$, lowest $K = 139.27$, $P < 0.0001$). However, there were no significant differences in the uterine artery PI-MoM values between monochorionic and dichorionic twins. The uterine artery PI in twin pregnancies that developed early-onset PE ($P < 0.001$) and SGA of both twins ($P < 0.05$) was higher than the uterine artery PI in uncomplicated twin pregnancies, whereas no differences were found for late PE or SGA of one twin.

Conclusions First-trimester placental impedance to flow, as assessed by uterine artery Doppler examination, is reduced in twin pregnancies, with no differences related to chorionicity. The relative increase of uterine artery PI found in twin pregnancies that developed early PE and SGA of both twins suggests that first-trimester uterine artery assessment may be useful in identifying such complications. Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Pre-eclampsia (PE) affects 2% of all pregnancies and is one of the major causes of maternal and perinatal mortality and morbidity¹. The pathophysiology of PE is still poorly understood although it is thought to be the consequence of impaired trophoblastic invasion of maternal spiral arteries, resulting in placental hypoxia and release of factors leading to maternal endothelial dysfunction, with subsequent hypertension and proteinuria². The impaired trophoblastic invasion may be assessed by Doppler studies of the uterine arteries and several studies have provided evidence of an association between increased impedance to flow in uterine artery present from the first trimester of pregnancy and subsequent PE^{3,4}.

Twin pregnancies present a higher incidence of PE when compared with singleton gestations^{5–7}. Doppler studies performed in the second trimester have reported an increased impedance to flow in the uterine artery of twin pregnancies that developed PE compared with twin pregnancies not developing PE^{8–10}. No data exist, however, on uterine artery Doppler waveforms during the first trimester in twin pregnancies. Early recognition of impaired placental perfusion is of great clinical interest because it may enable an early start of prophylactic treatments, which are potentially more effective than those started in the second trimester.

The objective of this study was to compare uterine artery impedance to flow between twin and singleton pregnancies and to assess the differences, if any, between twin pregnancies who developed PE and those unaffected by this complication.

METHODS

Twin pregnancies attending the 11 + 0 to 13 + 6-week sonographic scan from January 2008 to January 2013 were considered for this study. All women with two live fetuses and no obvious major fetal abnormalities were

Correspondence to: Prof. G. Rizzo, Department of Obstetrics and Gynecology, Università di Roma Tor Vergata, Ospedale 'Fatebenefratelli S. Giovanni Calabita', IsolaTiberina 89, 00186 Rome, Italy (e-mail: giuseppe.rizzo@uniroma2.it)

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offered the option of a uterine artery Doppler study as a method of screening for PE. These criteria were fulfilled in 452 twin pregnancies. The study was approved by the local Ethics Committee and written informed consent was obtained from all participating women.

Chorionicity was determined according to the presence or absence of an extension of placental tissue into the base of the intertwin membrane, visualized sonographically as the lambda sign in dichorionic twin pregnancies and as the T-sign in monochorionic twins¹¹. Gestational age was calculated on the basis of the last menstrual period. Pregnancies were redated by measurement of the crown–rump length (CRL) of the larger twin if the discrepancy was more than 7 days¹².

Data on pregnancy outcome were obtained from examination of individual patients' hospital records. Outcome measures were early-onset PE requiring delivery at < 34 weeks' gestation and late-onset PE delivering after ≥ 34 weeks, and small-for-gestational age (SGA) < 5th centile as a birth weight of one or both twins. As a control group we considered 500 singleton pregnancies extracted from our database that underwent, at our institution, the 11 + 0 to 13 + 6-week scan and uterine artery Doppler velocity waveform recordings, and that were free from fetal structural and chromosomal abnormalities and had known normal perinatal outcome.

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy¹³. In PE, the diastolic blood pressure should be ≥ 90 mmHg on at least two occasions, 4 h apart, developing after 20 weeks of gestation in previously normotensive women, together with the presence of significant proteinuria (≥ 300 mg in 24 h, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection was available). Birth-weight percentiles were calculated using a reference range derived from our population¹⁴.

Uterine artery velocity waveforms were recorded trans-abdominally (Voluson E8; GE Healthcare Ultrasound,

Milwaukee, WI, USA) using a previously described technique¹⁵ and following The Fetal Medicine Foundation's guidelines¹⁶. Briefly, a sagittal section of the uterus was obtained and the cervical canal and internal cervical os were identified. The transducer was then gently tilted from side to side and color flow mapping was used to identify each uterine artery adjacent to the cervix and uterus at the level of the internal os. Pulsed wave Doppler was used with the sampling gate set at 2 mm to cover the whole vessel and care was taken to ensure that the angle of insonation was < 30°. When three similar consecutive waveforms were obtained, the pulsatility index (PI) was measured and the mean PI of the left and right arteries was calculated. We considered also the lowest uterine artery PI value because there is evidence, in singleton pregnancies, of a predictive value of this index for PE and SGA^{17,18}.

In each pregnancy the mean and the lowest uterine artery PI were expressed as a multiple of the expected median calculated from The Fetal Medicine Foundation's reference limits for singleton pregnancies after correction for gestational age and maternal ethnicity and body mass index (BMI)¹⁹.

In order to generate MoMs specific for twin pregnancies, a regression analysis was performed between the mean and lowest uterine artery PI values and CRL values of the larger twin in uncomplicated pregnancies. Uterine artery PI values were then converted as MoM of the expected values for twins, and comparison were performed between uncomplicated pregnancies and those complicated by PE and/or SGA.

Maternal and fetal characteristics were compared using the chi-square test for categorical variables, whereas continuous variables were compared using the Kruskal–Wallis test or the Mann–Whitney *U*-test, as appropriate. $P < 0.05$ was considered as significant. The statistical software package SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used for data analyses.

Table 1 Maternal and pregnancy characteristics of the study population

Characteristic	Singleton (n = 500)	Dichorionic (n = 384)	Monochorionic (n = 37)	P
Maternal age at screening (years)	31.4 (18–44)	32.7 (20–46)	30.6 (19–39)	0.877
Gestational age at screening (days)	86 (79–92)	87 (77–96)	85 (81–93)	0.926
Nulliparous	254 (50.8)	193 (50.3)	18 (48.6)	0.962
BMI (kg/m ²)	25.6 (16.2–43.6)	26.2 (17.8–44.5)	25.7 (19.3–36.8)	0.951
Ethnicity				0.724
Caucasian	461 (92.2)	357 (93.0)	32 (86.5)	
African	10 (2.0)	9 (2.3)	2 (5.4)	
East Asian	26 (5.2)	16 (4.2)	3 (8.1)	
Mixed	3 (0.6)	2 (0.6)	0 (0)	
Cigarette smoking	38 (7.6)	28 (7.2)	3 (8.1)	0.975
Cesarean section	127 (25.4)	283 (73.7)	36 (97.3)	< 0.0001
Early-onset PE	3 (0.6)	6 (1.6)	2 (5.4)	0.02
Late-onset PE	9 (1.8)	22 (5.7)	2 (5.4)	0.006
SGA both twins		36 (9.4)	3 (8.1)	0.800
SGA one twin		82 (21.4)	9 (24.3)	0.675

Values are given as *n* (%) or median (range). BMI, body mass index; PE, pre-eclampsia; SGA, small-for-gestational age.

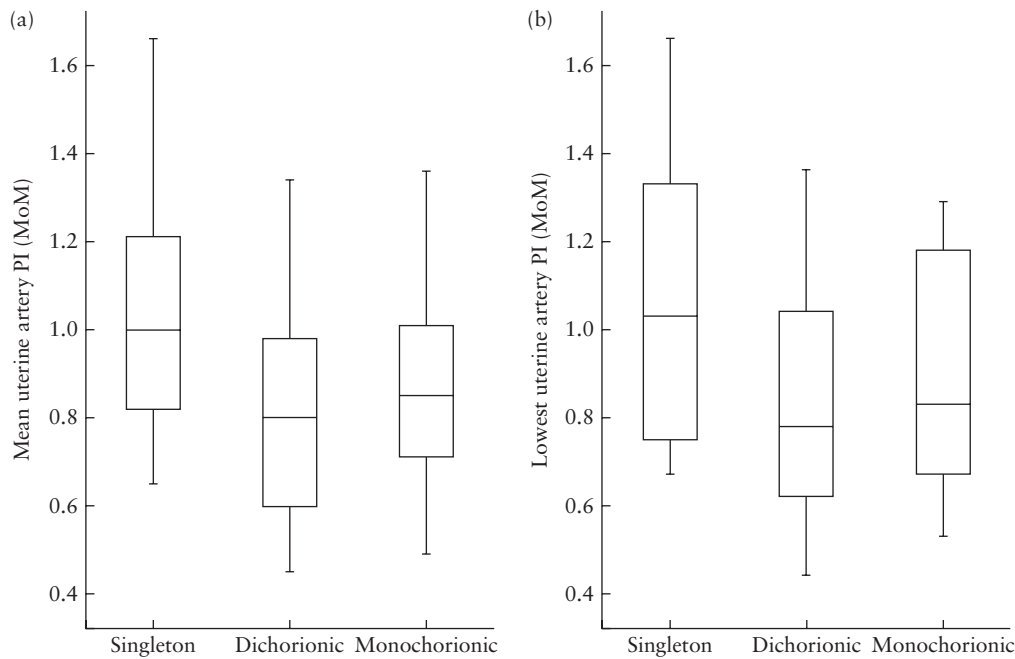


Figure 1 Box-and-whisker plots of mean (a) and lowest (b) uterine artery pulsatility index (PI) multiples of the expected median (MoM) values in singleton and twin pregnancies. Boxes show median and interquartile range, and whiskers represent minimum and maximum values.

RESULTS

Doppler examination of the uterine arteries was carried out in 452 twin pregnancies, of which 409 were dichorionic and 43 were mono chorionic diamniotic. We excluded, from further analysis, 18 (3.9%) cases for lack of or incomplete data on pregnancy outcome and 13 (2.9%) because of prenatal or postnatal diagnosis of twin-to-twin transfusion syndrome, aneuploidies or major defects. Complete outcome data were therefore available in 421 twin pregnancies of the total group (384 dichorionic and 37 mono chorionic), and this constituted the study population.

Characteristics of the study population and control group of singleton pregnancies are shown in Table 1. The incidence of both early- and late-onset PE was significantly higher in twin pregnancies, and there were no significant differences between mono chorionic and dichorionic pregnancies. Likewise, the incidence of SGA of one or both fetuses was similar in the two twin groups.

The mean uterine artery PI MoM was significantly lower in both twin groups when compared with singleton pregnancies (median uterine artery PI MoM = 1.0 (interquartile range (IQR), 0.82–1.21) in singleton pregnancies; Kruskal–Wallis test for the three groups: $K = 174.31$, $P < 0.0001$). However, there were no differences in PI MoM values between dichorionic (median = 0.80 (IQR, 0.60–0.98)) and mono chorionic (median = 0.85 (IQR, 0.71–1.01); $P = 0.122$) pregnancies (Figure 1a). Similarly, the lowest uterine artery PI values were lower in twin pregnancies (median uterine artery PI = 1.03 (IQR, 0.75–1.33) in singleton pregnancies; Kruskal–Wallis test for the three groups $K = 139.27$, $P < 0.0001$)

and there was no difference for chorionicity (dichorionic: median = 0.78 (IQR, 0.62–1.04); mono chorionic: median = 0.83 (IQR, 0.67–1.18); $P = 0.096$) (Figure 1b).

The median mean and lowest uterine artery PI MoM values calculated from singleton nomograms were significantly higher in both twin groups in the presence of early-onset PE (median mean MoM = 1.13 (IQR, 1.06–1.19), $P < 0.001$; median lowest MoM = 1.09 (IQR, 0.98–1.18), $P < 0.001$) and SGA of both twins (median mean MoM = 0.99 (IQR, 0.91–1.08), $P = 0.024$; median lowest MoM = 1.03 (IQR, 0.89–1.14), $P = 0.029$) than in uncomplicated twin pregnancies (median mean PI = 0.71 (IQR, 0.58–0.85); median lowest MoM = 0.74 (IQR, 0.53–0.92). No differences in uterine artery PI MoM were found in the presence of late PE (mean PI, $P = 0.33$; lowest PI, $P = 0.39$) or SGA of a single twin (mean PI, $P = 0.47$; lowest PI, $P = 0.55$) (Figure 2).

These findings were also confirmed when MoMs were calculated from the uncomplicated twin cohort of this study. Median mean and lowest PI MoM values were significantly higher in pregnancies complicated by early PE and SGA of both twins, but not in the presence of late PE and SGA of one twin, as shown in Table 2.

DISCUSSION

The findings of this study demonstrate that twin pregnancies are associated with an increased risk of developing early- or late-onset PE and SGA of one or both twins. This is consistent with previous reports showing higher incidences of such complications in twin pregnancies^{5–7,20}. Similarly, the absence of significant differences in the incidence of these complications when related to chorionicity is in keeping with previous

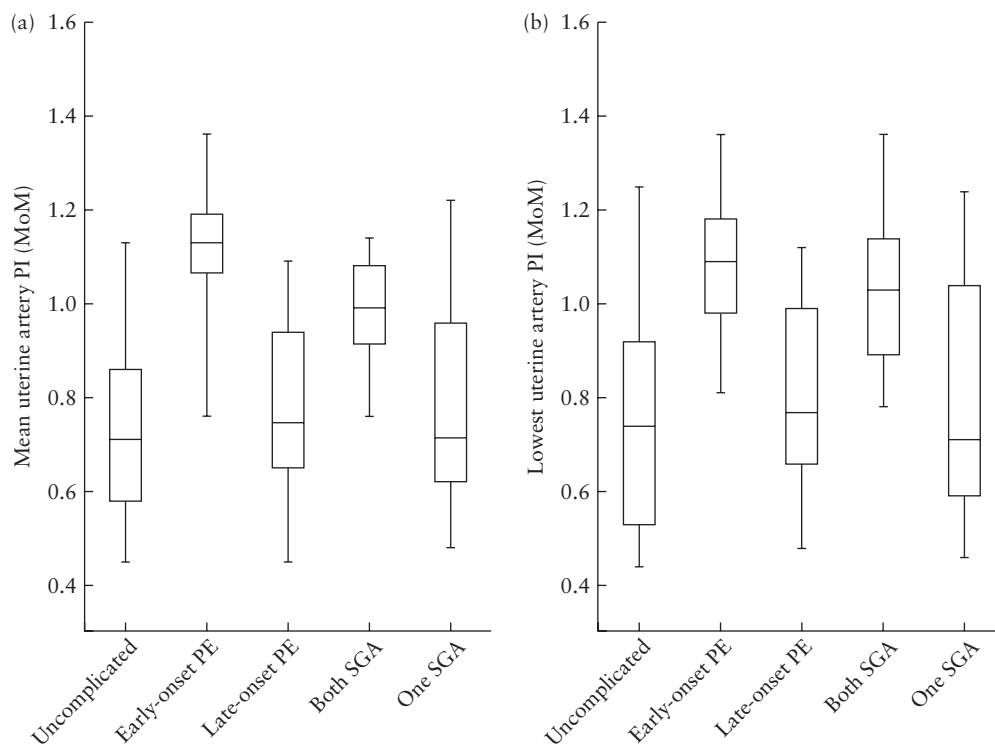


Figure 2 Box-and-whisker plots of mean (a) and lowest (b) uterine artery pulsatility index (PI) multiples of the expected median (MoM) values in twin pregnancies grouped according to outcome. MoMs were calculated from singleton nomograms. Boxes show median and interquartile range, and whiskers represent minimum and maximum values. PE, pre-eclampsia; SGA, small-for-gestational age.

Table 2 Uterine artery pulsatility index (UtA-PI) multiple of the expected median (MoM) values in the different outcome groups

Outcome group	Mean UtA-PI MoM	Lowest UtA-PI MoM
Uncomplicated	1.01 (0.84–1.25)	1.0 (0.83–1.27)
Early-onset PE	1.46 (1.11–1.71)*	1.41 (1.09–1.63)*
Late-onset PE	1.22 (0.87–1.39)	1.18 (0.86–1.41)
SGA both twins	1.39 (1.07–1.57)†	1.38 (1.09–1.46)†
SGA one twin	1.09 (0.86–1.31)	1.06 (0.85–1.33)

Values are median (interquartile range). MoMs were calculated from the uncomplicated twin cohort. * $P < 0.001$, † $P < 0.05$: *vs* uncomplicated, Mann–Whitney *U*-test. PE, pre-eclampsia, SGA, small-for-gestational age.

reports analyzing their prevalence in both twin pregnancy groups, after excluding those complicated by twin-to-twin transfusion syndrome^{9,21}.

This study also demonstrates that in twin pregnancies the uterine artery PI at 11 + 0 to 13 + 6 weeks of gestation is lower than in singleton pregnancies, a finding consistent with previous reports from ourselves and others, obtained at 20–24 weeks^{8,22,23}. The overall lower PI values may reflect the larger placental implantation site present in twin pregnancies and the different hemodynamic maternal status occurring in this condition. Furthermore, in agreement with late second-trimester findings⁹, there are no differences in uterine artery PI values between monochorionic and dichorionic pregnancies, suggesting that the total placental size, rather than genetic or hormonal factors that may differ with chorionicity, are likely to play the major role in uterine impedance to flow²⁴.

We also observed that uterine artery PI is increased in the presence of early-onset PE but not in the presence of late-onset PE. Although our definition of SGA was based on singleton charts that may bias their incidence, we also found an association between increased uterine artery PI and SGA of both twins but not when there was SGA of only one twin.

These findings are in agreement with the results obtained in singleton pregnancies during the first and second trimesters, showing that uterine artery Doppler is particularly effective in identifying women who develop severe early-onset PE rather than late-onset diseases^{3,4}. Indeed, pathological studies have demonstrated that the prevalence of placental lesions in singleton pregnancies with PE is inversely related to the gestational age at delivery²⁵. As there is no evidence that the process of placentation is significantly different in twin *vs* singleton pregnancies, in terms of trophoblastic invasion and its timing²⁴, it is logical to suppose that the same mechanisms may occur in multiple pregnancies.

The relatively low number of twin pregnancies considered in this study does not allow us to calculate the ability of uterine artery PI in predicting early-onset PE and SGA of both twins. Similarly, we cannot establish whether the lowest or the mean value of uterine artery PI is most useful. However, the degree of overlap in PI values observed in this study between pregnancies who did or did not develop these complications suggests a limited role in the isolated use of first-trimester uterine artery Doppler as a screening tool. In singleton pregnancies, effective screening for PE was achieved only with the

combination of maternal variables, uterine artery Doppler and biochemical markers^{18,26}. A similar approach should be applied also to a larger population of twin pregnancies.

Finally, the importance of first-trimester identification of twin pregnancies at higher risk of developing early-onset diseases should be underlined because these conditions are associated with an increased risk of perinatal mortality and morbidity and both short- and long-term maternal complications that deserve targeted antenatal care and surveillance. Furthermore, the identification of these high-risk twin pregnancies during the first trimester could form the basis of therapeutic interventions starting early in pregnancy. In singleton pregnancies this approach has already proved to be more effective than treatment instituted later during the second trimester^{27,28}.

In conclusion, in twin pregnancies PI in the uterine arteries during the first trimester is lower than in singleton pregnancies, and there are no significant differences between dichorionic and monochorionic pregnancies. Doppler assessment of the uterine arteries at 11+0 to 13+6 weeks may be useful to identify twin pregnancies destined to develop severe complications related to uteroplacental insufficiency.

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