

Reference ranges for Doppler assessment of uterine artery resistance and pulsatility indices in dichorionic twin pregnancies

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ABSTRACT

Objectives To construct reference ranges of uterine artery Doppler parameters against gestation in twin pregnancies and to present charts of the pulsatility index (PI) and resistance index (RI) for clinical use.

Methods This was an observational study of the uterine circulation in 557 women with dichorionic twin pregnancies at 17–38 weeks' gestation. Uterine artery measurements were performed by color and pulsed Doppler imaging. The uterine artery PI and RI were calculated as a mean of both sides. Reference ranges were constructed by regression of each index on gestational age. For this purpose, a regression model with fractional polynomials was fitted to the data. Furthermore, the presence of uterine artery notching was recorded.

Results New reference curves and tables of percentiles of the uterine artery PI and RI are presented. The calculated indices both showed a significant decrease with gestational age. Compared with singleton values, mean twin PI values were lower during the whole course of pregnancy. The prevalence of bilateral notching was 4.6% at 17–19 weeks' gestation and 3.1% at 20–24 weeks.

Conclusions Uterine artery Doppler indices in twin pregnancies are lower than in singleton pregnancies. Therefore, the use of uterine artery reference ranges adapted to twin gestations seems more appropriate for identifying low- and high-risk groups. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

With the increase in maternal age and the frequent employment of assisted reproductive procedures, obstetricians face a growing number of twin pregnancies, which differ from singleton pregnancies with respect to mean duration of pregnancy and birth weight. They are at increased risk for numerous fetal and maternal complications, which are often related to impaired uteroplacental function, i.e. preterm delivery, fetal growth restriction, stillbirth, gestational hypertension and pre-eclampsia^{1–5}. The frequency of adverse pregnancy outcome is much higher in monochorionic than in dichorionic gestations, but neither the sex of the offspring nor zygosity seems to influence the incidence of hypertensive disease^{4,6}.

Routine investigation of midtrimester uterine artery flow velocity waveforms by Doppler examination in singleton pregnancies may be a useful predictor of uteroplacental complications such as pre-eclampsia, intrauterine growth restriction (IUGR), stillbirth and placental abruption^{7–12}. The clinical benefit in particular is the identification of the most severe cases, which require delivery before 34 weeks' gestation^{9,12–15}. Doppler interrogation of the uterine artery also has its place in the late second or third trimester as an indicator of increased risk for adverse outcome^{16,17}.

As multiple pregnancies constitute a high-risk group for antenatal care, measurement of uterine artery Doppler indices could be useful in the prediction of uteroplacental dysfunction. In recent studies the performance of uterine Doppler investigation in the prediction of pre-eclampsia and IUGR was slightly poorer for twins than for

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singletons^{18,19}. However, it could be speculated that this method also identifies pregnancies that are at the highest risk for adverse outcome and that might benefit from increased antenatal surveillance.

The larger size of placental implantation in twins presumably contributes to a lower mean uterine artery resistance than in singletons^{18,19}. Therefore if reference ranges for singleton pregnancies are applied to the assessment of twin pregnancies, a higher rate of false-negative findings can be expected¹⁹.

To date, only limited data on uterine artery Doppler investigations in twins are available. The aim of this study was to construct reference values for the second and third-trimester pulsatility index (PI) and resistance index (RI) in twin pregnancies for clinical use and to compare these data with published normative values for singleton pregnancies.

METHODS

This was an observational study of 557 women with dichorionic twin pregnancies and follow-up available at 17–38 weeks' gestation, recruited from our routine antenatal clinic between July 1998 and January 2006. Inclusion criteria were: confirmed gestational age and chorionicity by first-trimester examination, two live fetuses and absence of maternal complications (diabetes, hypertension, pre-eclampsia) and fetal complications (major abnormalities, growth restriction) at the time of evaluation. Doppler measurements of the uterine arteries were obtained transabdominally by appropriately trained examiners. After identification of the uterine artery at the crossing with the external iliac artery⁹ by means of color Doppler sonography, pulsed-wave Doppler was used to obtain at least three similar flow velocity waveforms for each side. The uterine artery PI and RI were calculated as a mean of both sides and the presence of early diastolic notching was recorded. In total 990 measurements were obtained for the PI and 667 measurements for the RI. Of those, 555 measurements (one measurement per pregnancy) for the PI and 396 for the RI (one measurement per pregnancy) were utilized for the calculation of reference curves. If there was more than one measurement per case we chose the one with the lowest gestational age. Demographic characteristics, Doppler parameters and outcome data were stored in a computer database.

Statistical analysis

To estimate reference intervals for the PI and RI we used the method proposed by Royston and Wright²⁰. Curves for the mean values were obtained by fitting fractional polynomials to the data²¹. For PI this was done after a logarithmic transformation of the data to correct for the skewness of the data around the median for each gestational age. For both variables a degree-1 fractional polynomial of the form $a + b/g^2$, where g is gestational age and a and b are regression coefficients, was found to be the best fitting polynomial. Since for both variables the variation of the observations around the estimated mean curve

did not depend on gestational age, the curves for the 5th and 95th centiles were constructed by subtracting/adding $1.645 \times \text{SD}$ to the mean curve, where SD is the square root of the residual variance. The calculations were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Reference charts for uterine artery PI and RI in twin pregnancies were constructed and the individual twin values for PI were compared with established singleton charts²².

RESULTS

A total of 557 twin pregnancies with measurement of uterine artery PI and/or RI were included in the study. The mean maternal age was 31.9 ± 4.8 years, and 43.1% were nulliparous. The majority (>95%) were Caucasian. The mean gestational age at delivery was 36.3 ± 2.5 weeks (including 8.7% preterm deliveries before 32 weeks). The mean birth weight was 2350 ± 537 g and the mean birth-weight discordance was 12.7%. Birth weight < 10th centile of at least one fetus occurred in 17.7%²³. Pre-eclampsia was observed in 6.3% (35/557).

Results of polynomial regression analysis with the curve-fitted reference charts for PI and RI are shown in Figures 1 and 2. The calculated regression lines were expressed by the equations:

$$\ln \text{PI} = -0.6675 + 186.1/g^2; \text{SD} = 0.263 \text{ and}$$

$$\text{RI} = 0.3988 + 51.77/g^2; \text{SD} = 0.0853.$$

Gestational-age-specific reference values for the 5th, 50th and 95th centiles of the PI and RI are presented in Tables 1 and 2. Uterine artery waveform PI and RI both showed a decrease with advancing gestation. Bilateral notching was observed in 4.6% at 17–19 weeks, 3.1% at 20–24 weeks, 3.0% at 25–28 weeks, 1.8% at 29–32 weeks and 0.6% at 33–38 weeks.

Figure 3 shows the individual uterine artery PI values of twin pregnancies plotted on singleton reference curves of Gómez *et al.*²². The figure demonstrates that the majority of values for twins were below the 50th centile for singletons and 27% of values were below the 5th centile. Only 2.3% of values were above the 95th centile. Therefore, singleton references seem inadequate for the evaluation of twin pregnancy uterine artery resistance.

DISCUSSION

Our study presents new reference charts of uterine artery PI and RI against gestation in dichorionic twin pregnancies. The data used to construct the reference ranges represent our measurements used in clinical practice. To avoid the investigation of a non-representative population, all pregnancies with a normal course of pregnancy at the time of ultrasound evaluation have been included²⁴.

Our study found a continuous decrease in both RI and PI between 17 and 38 weeks' gestation. The decrease was steeper until 32 weeks and thereafter shallower until 38 weeks. The findings for RI are consistent with those

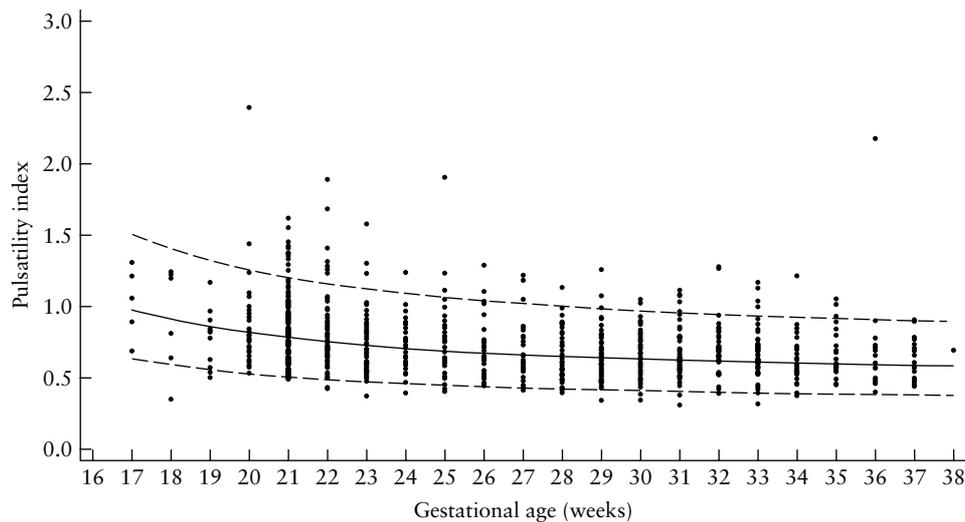


Figure 1 Individual values ($n = 990$) of uterine artery pulsatility index, including repeat measurements, plotted on the reference range (5th, 50th and 95th centiles) constructed from cross-sectional data obtained in 555 women with twin pregnancies.

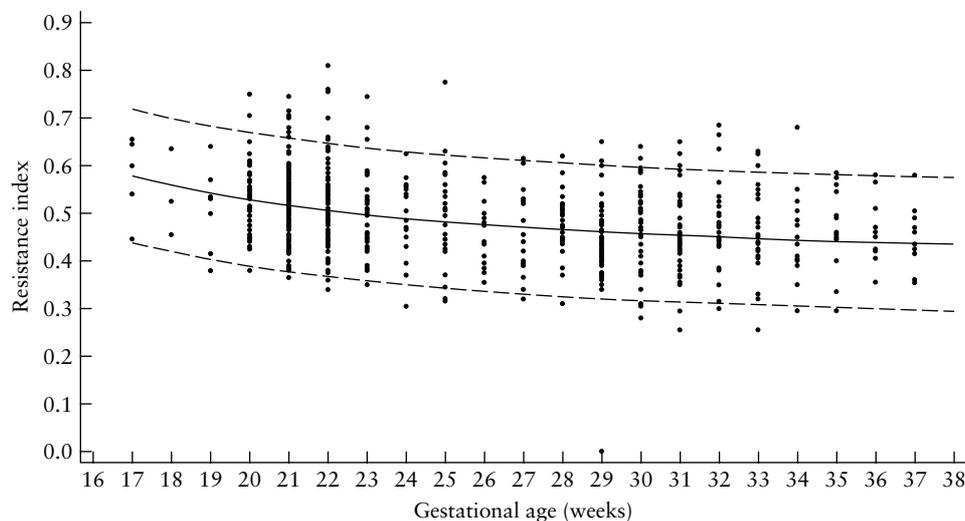


Figure 2 Individual values ($n = 667$) of uterine artery resistance index, including repeat measurements, plotted on the reference range (5th, 50th and 95th centiles) constructed from cross-sectional data obtained in 396 women with twin pregnancies.

of other small studies²⁵, but are in contrast to the results of Chen *et al.*²⁶, who found a decrease in uterine artery PI only until 27 weeks' gestation, with unchanged values thereafter. However, the latter study included Doppler measurements of only 34 uncomplicated twin pregnancies.

Uterine artery resistance is thought to reflect the hemodynamic changes of trophoblastic invasion. We have confirmed the results of previous studies demonstrating lower mean RIs in both uterine arteries in twin pregnancies than in singleton pregnancies^{18,19,25,26}. A straightforward explanation for this observation is the combined larger implantation site of the two placentas. Rizzo *et al.*²⁵ further suggested that the two placental low-resistance circuits connected in parallel are an additive cause of the greater fall in uterine vascular resistance. Figure 3 illustrates the difference in PI between established singletons values²² and our twin values. We would like to emphasize that most values were below the 50th centile, and 27%

of twin scatter plots were even below the 5th centile of singleton references. The use of singleton references would therefore result in the false-negative classification of a certain number of twin pregnancies into a low-risk group. Likewise, a previous study with assessment of the uterine artery RI in twin pregnancies at 18–24 weeks found only 3.1% of the measurements above the 95th centile of the singleton reference charts¹⁹.

The screening performance of Doppler ultrasound studies of the uteroplacental circulation is affected by many variables, for instance gestational age at examination and, indeed, the definition of abnormality. A recent review considered an increased PI with notching in the second trimester as the best overall predictor of pre-eclampsia in low-risk and high-risk patients¹¹. With respect to several cut-offs used in singletons at 22–24 weeks, the reported PI values for the 95th centile range from 1.41 to 1.63^{12,13,15,22}. In the twin study of Yu *et al.*¹⁸, between 22 and 24 weeks' gestation the 95th centile of the PI was

Table 1 Uterine artery pulsatility index based on 555 measurements in twin gestations

GA (weeks)	n	5 th centile	50 th centile	95 th centile
17	5	0.635	0.977	1.505
18	7	0.592	0.912	1.404
19	10	0.558	0.859	1.324
20	47	0.531	0.817	1.259
21	152	0.508	0.783	1.206
22	104	0.489	0.754	1.161
23	52	0.474	0.730	1.124
24	19	0.460	0.709	1.092
25	18	0.449	0.691	1.065
26	20	0.439	0.676	1.041
27	13	0.430	0.662	1.020
28	22	0.422	0.651	1.002
29	17	0.416	0.640	0.986
30	17	0.410	0.631	0.972
31	10	0.404	0.623	0.959
32	13	0.399	0.615	0.948
33	6	0.395	0.609	0.938
34	7	0.391	0.603	0.928
35	9	0.388	0.597	0.920
36	1	0.385	0.592	0.912
37	5	0.382	0.588	0.905
38	1	0.379	0.584	0.899

GA, gestational age.

1.5, which is considerably higher than our value for this gestational age (1.13), and lies in the range of reported singleton references. They included monochorionic and dichorionic pregnancies, as there was no difference in uterine artery PI from 22 to 24 weeks between the two chorionicity groups¹⁸.

Together with the fall in uterine artery resistance with gestation, we observed a progressive decline in the prevalence of bilateral notching in twin pregnancies. While in the earlier second trimester this finding was present in 4.6% of pregnancies, it decreased to 1.8% at 29–32 weeks and was rarely observed afterwards. Compared to the findings of singleton studies,

Table 2 Uterine artery resistance index based on 396 measurements in twin gestations

GA (weeks)	n	5 th centile	50 th centile	95 th centile
17	5	0.438	0.578	0.718
18	4	0.418	0.559	0.699
19	6	0.402	0.542	0.683
20	42	0.388	0.528	0.669
21	128	0.376	0.516	0.657
22	83	0.365	0.506	0.646
23	32	0.356	0.497	0.637
24	7	0.348	0.489	0.629
25	10	0.341	0.482	0.622
26	13	0.335	0.475	0.616
27	6	0.329	0.470	0.610
28	6	0.324	0.465	0.605
29	10	0.320	0.460	0.601
30	14	0.316	0.456	0.597
31	5	0.312	0.453	0.593
32	7	0.309	0.449	0.590
33	4	0.306	0.446	0.587
34	4	0.303	0.444	0.584
35	5	0.301	0.441	0.581
36	2	0.298	0.439	0.579
37	3	0.296	0.437	0.577
38	0	0.294	0.435	0.575

GA, gestational age.

where bilateral notching at around 20 weeks' gestation is reported in 9–12%^{13,27}, the prevalence in our study and the one of Yu *et al.*¹⁸ is lower, at 3.1% and 3.4%, respectively.

Several physiological effects of twin pregnancies may alter maternofetal hemodynamics and therefore affect the screening performance of uterine artery Doppler investigations. Although the test identified a considerable proportion of pregnancies with prospective adverse outcome, the sensitivity of the test was lower than for singleton pregnancies^{18,19}. Recent studies on twin pregnancies utilizing twin references reported sensitivities of 30–40% and 10–20% for the prediction of

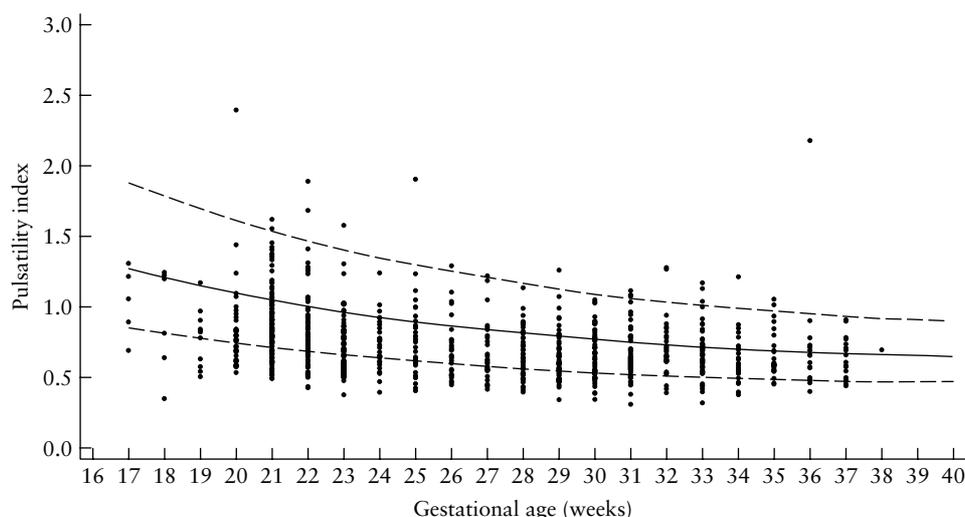


Figure 3 Individual uterine artery pulsatility index values ($n = 990$) of twin pregnancies plotted on singleton reference curves (5th, 50th and 95th centiles) of Gómez *et al.*²². Of note, 27% of twin scatter plots are below the 5th centile and only 2.3% of twin scatter plots are above the 95th centile of singleton references.

pre-eclampsia and growth restriction, respectively^{18,19}. The results of these studies also demonstrate the higher sensitivity of mean PI or RI than the presence of bilateral notches in the prediction of adverse outcome caused by uteroplacental insufficiency^{18,19}. However, women that present both increased uterine artery resistance and bilateral notches constitute an even higher-risk group.

In the third trimester of pregnancy uterine artery Doppler sonography is an additional tool for evaluating patients with the clinical manifestations of pre-eclampsia and fetuses with growth restriction. In singletons, increased uterine artery resistance in the third trimester was related to increased risk of adverse neonatal outcome^{16,17,28}. It can be assumed that this method could be also helpful in the evaluation of complicated twin gestations.

In summary, we have established new reference ranges for uterine artery PI and RI in twin pregnancies. The use of these references is recommended for assessment of the second- and third-trimester uteroplacental circulation in twins in order to aid risk stratification and for the timing of antenatal care. Further studies should focus on the clinical value of these indices, i.e. identification of the most severe cases with pre-eclampsia and/or IUGR with the need for early preterm delivery.

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