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Doppler Velocimetry of the Ophthalmic Artery Behavior in Twin Pregnancy

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Abstract: Our main objective was to evaluate the ophthalmic artery Doppler behavior in twin pregnancies and compare with singleton pregnancies. We studied 64 healthy twin pregnant women between 12 to 38 weeks of gestation. Resistance index (RI), pulsatility index (PI), and peak ratio (PR) were determined. The control group consisted of 289 singletons. Linear regression analysis was performed to evaluate the association between gestational age and the ophthalmic indexes. Student *t* test was used to compare the means and standard deviation of the Doppler indexes. There was a decrease in RI and PI and an increase in PR with advancing gestational age ($\rho < 0.0001$, 0.0052, and 0.0033). The means ± SDs for RI, PI, and PR were 0.77 ± 0.07, 1.79 ± 0.46, and 0.53 ± 0.12, in women with twin pregnancies and 0.75 ± 0.05, 1.88 ± 0.43, and 0.52 ± 0.10 in singletons. No significant difference was found between the PI and PR values, but significant difference was found in the RI values between the groups ($P = 0.0332$). We concluded that there are no significant differences in ophthalmic artery behavior in twins and the same reference values established in singleton pregnancies can be applied for PI and PR indexes in the evaluation of twin pregnancies. These indexes were the best to evaluate twin pregnancies.

Key Words: Doppler sonography, twin pregnancy, ophthalmic artery, pregnancy, reference values

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Hypertension is the most frequent clinical pregnancy complication and is a major cause of fetal, neonatal, and maternal complications worldwide. Twin pregnancy, by itself, is an independent risk factor for the development and exacerbation of hypertensive disorders.[1–5]

Increasing advances in assisted reproductive techniques and advanced maternal age have significantly contributed to the increased rate of multiple pregnancies, which has mostly occurred since the 1980s.[1,3,5–7]

Twin pregnancy is defined by the simultaneous presence of 2 fetuses in the mother's uterus. Twin pregnancy risks can be of maternal origin (anemia, gestational diabetes, hypertension, and early labor) and fetal origin (increased rates of genetic malformations, abnormal placentation, amniotic fluid disorders, discordant fetal growth restriction, and prematurity). Mortality rates in multiple pregnancies are high when compared with singleton pregnancies of the same gestational period, despite some improvements in antenatal care.[1,7] In 2009, perinatal mortality rates in twin pregnancies were 12.3/1000 compared with 5/1000 in singleton pregnancies.[8,9] Likewise, prematurity is also high (approximately 50%) in multiple gestations.[6–11]

Among the hypertensive syndromes that may affect pregnancy, preeclampsia (PE) presents the highest risk of maternal-fetus impairment. The chance of developing PE is 2.6 times higher in twin pregnancies than in singleton pregnancies, and twin-related PE is more severe and more frequently characterized as early onset PE.[1–5] It is concerning that at least 40% of multiple pregnancies result in the development of PE.[6,11,12]

Considering that the brain is a target organ for PE-induced injury and that hypertensive disorders are associated with poor maternal and fetal outcome, interest in the study of intracranial circulation has increased in patients with PE severity features. It is also important to establish differential diagnoses among hypertensive disorder classifications in pregnancy.[13–15] Ocular Doppler has shown to be a promising, highly accurate objective method in diagnosing the severity of preeclampsia, as well as helping in the differential diagnosis between preeclampsia and chronic hypertension. The analysis of the orbital vessels can assist in the evaluation of patients with hypertension during pregnancy.[16] It is considered a noninvasive, easily performed, and reproducible test.[17,18] However, there is no consensus on a reference for ophthalmic Doppler indexes for twin pregnancy, which are becoming a valuable instrument in the assessment of obstetric complications in twin pregnancy.[6,11,12]

Therefore, this study aimed to analyze the correlation between Doppler velocimetric indexes of the ophthalmic artery (resistance index [RI], pulsatility index [PI], and peak ratio [PR]) and the gestational age (GA) of patients with healthy twin pregnancies and to compare these data with singleton pregnancies.

METHODS

Healthy women with twin pregnancies (n = 64) with a GA between 12 and 38 weeks were evaluated in a cross-sectional

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observational study. Gestational age was calculated from the last menstrual period and confirmed by first trimester ultrasonography. As a standard established by the World Health Organization, the criterion of complete weeks was used. The studied population was characterized by women with twin pregnancies over 18 years of age, free of clinical complications or detectable diseases during the examination period, and with absence of labor. Exclusion criteria were smoking and abnormal uterine artery velocimetric findings (bilateral notch and/or RI higher than 0.55) after 24 weeks of gestation.[19] The control group consisted of 289 normotensive pregnant women.[20] Written informed consent was obtained from all selected patients, which was approved by the Ethics Committee in Research from the Maternity School at the Federal University of Rio de Janeiro.

Maternal blood pressure was measured during prenatal visits, before ocular Doppler sonographic assessment, with the patient seated after a rest period of 10 to 30 minutes. Normal blood pressure (BP) was considered as a systolic BP less than 140 mm Hg and diastolic BP less than 90 mm Hg.[20]

We used a NEMIO (Toshiba, Japan) ultrasound with pulsed and color Doppler and a 7.5-MHz linear transducer with a low-pass filter (50 Hz).[13,21]

Patients were examined in the supine position. Gel was applied to the closed eyelid, and the transducer was carefully placed on the eyelid to avoid creating pressure-derived artifacts. The blood flow waveform was easily obtained in the ophthalmic artery. The sample volume was adjusted to 2 to 3 mm and orientated nasally and superior to the optic nerve, just lateral to the visible hypoechoic stripe representing the nerve, nearly 12 to 15 mm from the posterior wall of the sclera. The angle of insonation of the ophthalmic artery remained less than 20 degrees (Fig. 1).[14,17,18,21–23] After obtaining 6 consecutive blood flow velocity waveforms with similar sizes and shapes, measurements were performed in a single waveform.[13,17,18,20–22,24,25] The RI, PI, and PR were determined by 2 measurements in the right eye (Fig. 2).

The mean time for analysis was approximately 5 minutes, not exceeding 15 minutes.[17]

All data underwent statistical analysis (S-PLUS version 8.0; TIBCO Software, Inc, Palo Alto, CA).

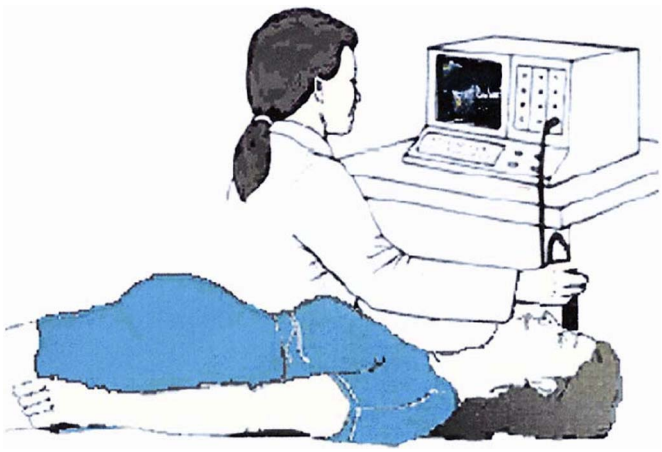

FIGURE 1. Linear regression between RI values and GA.

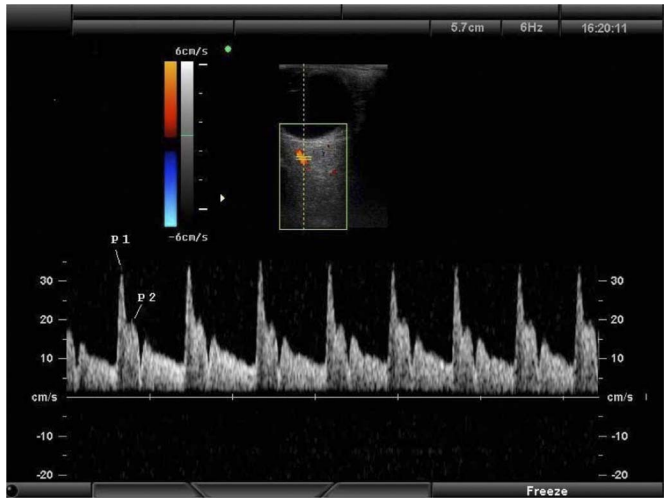

FIGURE 2. Linear regression between PI values and GA.

Linear regression analysis was performed to evaluate the association between GA and the means of the 2 measurements of ophthalmic indexes obtained in twin pregnancies.

No measurement of the left eye was performed, since previous studies reinforced no statistically significant differences in the data obtained from one side of the patient to the other.[13]

Student *t* test was used to compare the means and SDs of the Doppler indexes between twin and singleton pregnancies.

For all tests, a significance level of 0.05 and a power of 0.80 were set.

RESULTS

Sixty-four healthy women with twin pregnancies with mean ± SD GA of 27.5 ± 6.3 weeks were included in the study. Each week between 12 and 38 weeks of gestation was represented by approximately 2 patients.

The characteristics of the patients evaluated in each group are described in Table 1.

When the association between GA and the means of the ophthalmic artery Doppler indexes was analyzed by linear regression analysis, a statistically significant decrease in RI and PI values with advancing GA (ρ <0.0001 and 0.0052, respectively) was observed. An inverse correlation was observed between them (RI and PI with GA), with a decrease of 0.0237 RI units and 0.0056 PI units per week as the GA increased. However, there were low R^2 values for both indexes (0.2462 for RI and 0.119 for PI) (Table 2). Figures 3 and 4 show the linear regression plots between RI and GA and PI and GA, respectively.

When the association between GA and the means of the PR were analyzed by linear regression analysis, a statistically significant increase with advancing GA (ρ = 0.0033) was observed. A positive correlation was observed between PR and GA, with an increase of 0.0065 units in PR per week as the GA increased (Table 2). However, a low R^2 value was found (0.1307). Figure 5 shows the linear regression plot between PR values and GA.

When comparing Doppler indexes between twin and singleton pregnancies by Student *t* test, no significant difference was found for the PI and PR values (ρ = 0.1444 and 0.4811,

TABLE 1. Characteristics of the Study Participants

Group	Maternal Age, y	GA, wk	Systolic BP, mm Hg	Diastolic BP, mm Hg	No. Pregnancies	No. Previous Births
Twin pregnancy (n = 64)	27.5 ± 6.3	23.7 ± 6.7	113.8 ± 9.7	71.1 ± 9.6	2.0 ± 1.2	0.7 ± 0.8
Singleton pregnancy (n = 289)	28.2 ± 4.7	29.7 ± 6.2	100.1 ± 10.8	60.8 ± 11.0	2.0 ± 1.5	0.6 ± 1.0
P value	0.2928	<0.0001	<0.0001	<0.0001	0.8760	0.3775

Values are mean ± SD. $P > 0.05$ indicates no significant differences.

respectively). However, a statistically significant difference was found for the RI values between the groups ($P = 0.0332$). The mean RI in women with twin pregnancies was 0.02 units higher than the mean RI observed in singleton pregnancies.

The characteristics of the indexes evaluated in the groups and the results of the comparison of Doppler indexes between twin and singleton pregnancies by Student *t* test are described in Table 3.

DISCUSSION

Doppler use has expanded in all areas of medicine because of its wide range of information.[17] Doppler velocimetry of orbital vessels is not restricted to ophthalmology and is considered a noninvasive and reproducible test that can easily be performed by properly trained professionals.[17,18]

Ocular Doppler has proven to be an accurate method in assessing the severity of PE, as well as in the differential diagnosis of PE and chronic hypertension, in pregnant women,[13,14,22,25,26] representing a wide area for study and research that deserves increasingly more prominence in obstetrics.

Among pregnancies, twin pregnancies, with increasing rates over the past 30 years,[2,27] have been associated with higher morbidity and mortality compared with singleton pregnancies, demonstrating a higher incidence of perinatal complications, prematurity, and placental insufficiency.[2,15,27,28] Thus, several studies have sought to establish Doppler velocimetric parameters and references for risk assessment in twin pregnancy.

Although it is documented that greater care is needed in monitoring twin pregnancies, there is no consensus in the literature regarding the best parameters to use in the evaluation of maternal and fetal well-being. The vast majority of the references used in twin pregnancies are based on studies in singleton pregnancies and professional experience.[1,29]

It is increasingly necessary to deepen the knowledge of twin pregnancy for clarification and better understanding of hemodynamic alterations and the particularities of Doppler velocimetric parameters in these patients, as well as for establishing criteria for monitoring and evaluation, such as specific biometric tables, amniotic fluid volume, and diagnosis of pathological conditions.

The references found in the literature on the use of Doppler in twin pregnancy assess the uterine arteries, in most cases, to try to establish specific parameters for these vessels in this group of pregnant women.[28,30] In 2010 Geipel et al[30] studied the RI and PI of the uterine arteries in dichorionic twin pregnancies, trying to establish normality parameters. They observed a decrease in the RI and PI as GA increases, and comparing it with singleton pregnancies, PI values were lower throughout the course of twin pregnancy. In 2011, Klein et al[28] evaluated the average, lowest, and highest value of the PI of uterine arteries to screen for adverse pregnancy outcomes in twin pregnancies. Higher sensitivity and specificity for the risk of PE were observed with higher PI in twin pregnancy.

The high morbidity and mortality associated with PE arouse interest for new methods to better identify risk in PE patients. Doppler velocimetry of orbital vessels has emerged as a method of PE evaluation in singleton pregnancies, subsequently leading to the interest in this method for the evaluation of twin pregnancies because of their association with a high incidence of PE.

The present study evaluated the parameters of the ophthalmic artery Doppler velocimetry in healthy patients with twin

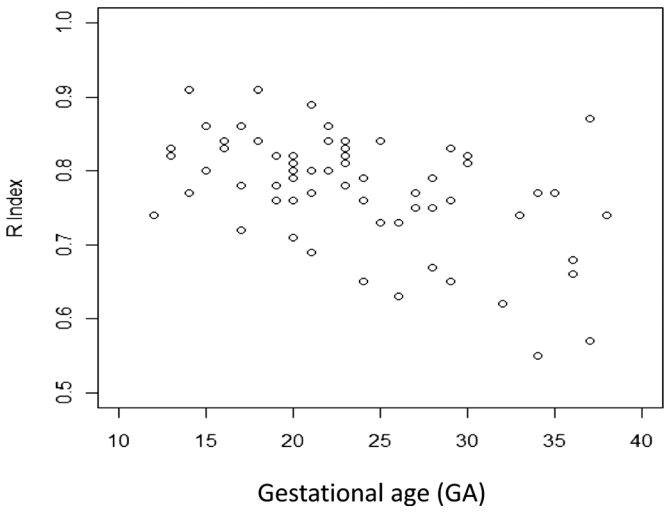

FIGURE 3. Linear regression between PR values and GA.

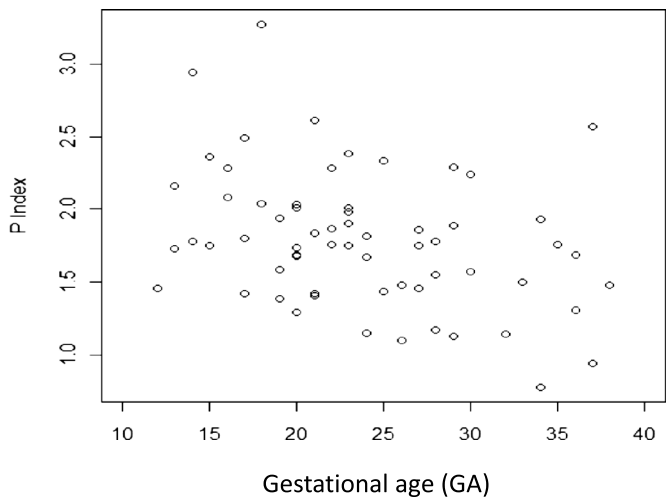

FIGURE 4.

TABLE 2. Association Between RI, PI, and PR in Twin Pregnancies and GA by Linear Regression Analysis

	Association	*P*	R^2	Modification of the Index
RI × GA	↓ RI with ↑ GA	$P < 0.0001$	0.2462	↓ 0.0237/wk
PI × GA	↓ PI with ↑ GA	$P = 0.0052$	0.119	↓ 0.0056/wk
PR × GA	↑ PR with ↑ GA	$P = 0.0033$	0.1307	↑ 0.0065/wk

n, number of healthy pregnant women. $P < 0.05$, significant.

TABLE 3. Ophthalmic Artery Doppler Indices of the Study Participants

	RI	PI	PR
Singleton pregnancy (n = 289)	0.75 ± 0.05	1.88 ± 0.43	0.52 ± 0.10
Twin pregnancy (n = 64)	0.77 ± 0.07	1.79 ± 0.46	0.53 ± 0.12
Student *t* test (*P* value)	0.0332	0.1444	0.4811

Values are mean ± SD. $P > 0.05$ indicates no significant differences.

pregnancies and compared these with the parameters observed in singleton pregnancies. Although statistically significant negative correlations were observed for the RI and PI with GA (the higher the GA, the lower the RI and PI) and statistically significant positive correlations were observed for the PR with GA (the higher the GA, the higher the PR), no reference values could be obtained for the indexes as a function of GA. Very low R^2 values were found in the linear regression analysis. Thus, only 24.6%, 11.9%, and 13% of the variations observed in the RI, PI, and PR, respectively, were associated with changes in GA. The R^2 values obtained suggest that there were other factors associated with the decrease in the RI and PI values and the increase in the PR values with advancing GA. Because the R^2 values were very low, the use of a normality curve would not appropriately represent the relationship between these indexes (RI, PI, and PR) and GA.

Moreover, the decrease in the RI and PI values and the increase in the PR values with advancing GA had no statistical relevance, allowing these indexes to be used in singleton as well as in twin pregnancies.

The PI and PR indexes proved to be the best indexes for evaluation of twin pregnancies, since no statistically significant differences were observed between the PI and PR mean values observed in women with twin pregnancies and those observed in women with singleton pregnancies. Therefore, the same reference values established for these indexes in singleton pregnancies can be used for evaluation of twin pregnancies in clinical practice. However, the same does not apply to RI values because a statistically significant difference was observed in the comparison of the groups (a higher RI mean was observed in twin pregnancies compared with singleton pregnancies).

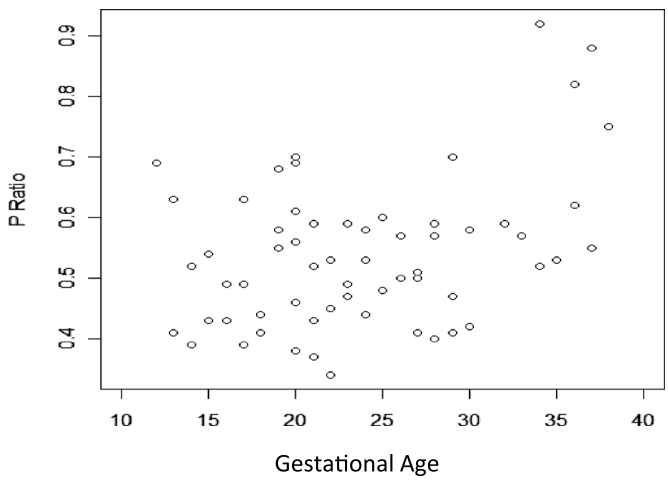

FIGURE 5.

The PR, an index proposed by Nakatsuka et al[16] in 2002 to evaluate ophthalmic artery flow, examines the rise in the wave flow velocity during mesodiastole quantifying specific changes of this type of wave in a better way.[17] Although the rising mechanism of this index is still not clear, the PR has been proposed as the most sensitive indicator of orbital vascular changes associated with changes in cerebral blood flow observed in PE.[17,18,31]

The ophthalmic artery Doppler velocimetry in twin pregnancy can be affected by different variables. Particular characteristics of twin pregnancy should also be considered, such as etiology (zygosity and chorionicity), placental weight and mass, related illnesses, and fertility treatment.

According to Campbell and MacGillivray[32] in 1999 and Savvidou et al[33] in 2001, the frequency of adverse outcomes in twin gestations is significantly higher in monochorionic pregnancies than in dichorionic pregnancies, including the risk of developing PE. However, the results found by Maxwell et al[27] in 2001 do not support the hypothesis that zygosity affects the rate of PE in twin pregnancies. In 2008, Bdolah et al[15] studied the risk of PE in twin pregnancy and observed a correlation between the increased risk of PE and the increase of placental mass, leading to an increase in circulating levels of plasma proteins in the maternal circulation.

In the future, more studies will be conducted that are aimed at the association between intracranial circulation and obstetric complications. Color Doppler velocimetry of orbital vessels has been shown to be a reliable method of assessment and is of great value when performed by trained professionals, which has increasingly been highlighted in research in different areas of medicine. This method deserves attention in the evaluation of patients who are at risk to improve the quality of assistance and follow-up of these patients, as it allows the indirect analysis of the blood flow at the level of intracranial circulation.

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