

# Can we measure the spiral and uterine artery blood flow by real-time sonography and Doppler indices to predict spontaneous miscarriage in a normal-risk population?

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## Abstract

*Introduction:* The predictive value of spiral artery flow Doppler measurements of a subsequent early miscarriage in first trimester pregnancy is explored here.

*Objective:* The aim of this study is to determine uterine and spiral artery blood flow changes in first trimester subsequent miscarriages and correlate within the mechanisms of the Doppler indices.

*Study design:* The uterine artery and spiral artery pulsatility and resistance indexes, systolic and diastolic ratios, acceleration times, and blood flow of both the right and left uterine arteries were obtained by trans vaginal color Doppler ultrasonography in consecutive viable pregnancies between 5 and 12 gestational week. Women were subsequently classified as having continuing pregnancies or pregnancy loss before 20 weeks gestation. To predict subsequent pregnancy loss, Doppler findings were adjusted for maternal age, history of previous abortion, presence of subchorionic hematoma, embryonic bradycardia, and gestational age by means of multivariate logistic regression analysis. The cut-off values are used for the ROC curve.

*Results:* Twenty-five pregnancies (11.7%) were spontaneously aborted before 20 weeks of gestational age. In 29 (13.6%) cases there were previously abortion history, 30 (14%) had bradycardia, and 37 (17.3%) had subchorionic hematoma. Regarding the parameters of uterine and spiral artery pulsatility and resistive index, acceleration time, systolic/diastolic ratios and blood flows, only uterine artery S/D low values were significantly associated with pregnancy loss in the multivariate logistic regression analysis ( $P = 0.0001$ , 95% CI: 4.968–55.675).

*Conclusion:* The uterine artery systolic/diastolic ratios have a predictive value for early pregnancy loss and seem to be useful as a marker. On the other hand, spiral artery changes could be so local that they cannot be determined by the parameters of spectral Doppler techniques. This suggests that uterine vascular bed alterations should be measured to understand the prognosis of early pregnancy loss during the first trimester.

*Keywords:* blood flow, early pregnancy, miscarriage, uterine artery, spiral artery, spectral Doppler.

## Introduction

Concern about the possibility of spontaneous miscarriage is one of the most common reasons women seek evaluation in the radiology department during their first trimester. Between 11% and 20% of all clinically recognised pregnancies are lost before the 20th week of gestation. Once a viable fetus is diagnosed by ultrasonography, however, the rate of spontaneous miscarriage subsequently decreases to 3% to 6%. The sonographic features associated with subsequent pregnancy loss have been previously described. These include embryonic bradycardia, subchorionic hematoma, irregular

gestational sac, first-trimester growth delay, and discrepancy between crown-rump length and sac volume.<sup>1,2</sup>

## Pathophysiology

The sequence of extravillous trophoblast invasion into the placental bed via the interstitial route into decidua and superficial myometrium (interstitial trophoblast) and through the lamina of spiral artery (endovascular trophoblast), with associated spiral artery changes, termed 'transformation' is well documented and appears to be a requirement for successful pregnancy.<sup>3,4</sup>

Alterations in the normal uterine perfusion

pattern have been noted in pregnancies complicated by blighted ovum and missed abortion. There is also evidence that increased intervillous blood flow at 7 to 12 weeks' gestation is associated with subsequent pregnancy failure. Despite the importance of uterine perfusion in the development of the growing conceptus, however, it is not known whether there are differences in uterine artery blood flow between continuing pregnancies and those that will miscarry after fetal cardiac activity has been documented.<sup>5,6</sup>

The vascular remodeling in the maternal-fetal interface may reduce local arterial resistance and thereby increase uteroplacental blood flow. Impairment of this process is associated with pregnancy complications including spontaneous abortion and placental hematoma, intrauterine growth restriction.<sup>7-10</sup>

### **The role of ultrasound**

With the advent of transvaginal color Doppler spiral sonography, new insights into uteroplacental circulation during the first trimester have been obtained. The use of Doppler sonography to analyse blood flow in even terminal branches of the uteroplacental circulation encouraged investigators to try and predict early and late pregnancy complications related to abnormal placentation.<sup>11</sup>

The uteroplacental circulation is a dynamic model in which the magnitude of blood flow through a single vessel may vary significantly, therefore the evaluation of blood flow in single uteroplacental vessels is often difficult to interpret and is of limited value in understanding the pathophysiology of placental-related disorders of pregnancy. Doppler ultrasound has been used for many years as a non-invasive technique to assess blood flow impedance. Although a number of studies have been reported regarding the change in uterine artery (UA) blood flow to assess uteroplacental circulation during early pregnancy, the findings given so far still seem to be controversial.<sup>12,13</sup>

However, the change in uterine artery and spiral artery blood flow during early pregnancy is also controversial. According to the literature that retrochorionic blood flow, which reflects spiral artery blood flow, increased progressively between the 4th and 12th week of pregnancy, the pulsatility index of the uterine artery decreased between the 5th and 10th week of pregnancy.<sup>14-16</sup> On the other hand, Bernstein, *et al.* reported that uterine blood flow did not significantly change between the 4th and 12th week of pregnancy.<sup>17</sup> Uterine vascular relaxation and the increase in uterine blood flow in early pregnancy appears to be important determinants of pregnancy outcome.

It is of interest to know whether blood flow impedance of spiral artery reflects vascular remodeling in the maternal-fetal interface at placentation, and whether abnormal blood flow patterns of spiral artery are associated with early pregnancy failure. Therefore, this study was undertaken to examine the change in blood flow impedance of the uterine artery and spiral artery during early pregnancy by highly sensitive Doppler indices.

### **Materials and methods**

The protocol of the study was approved by the Ethical Committee of the hospital and informed consent was obtained from the patients before their participation in this clinical study. The study was done in the Sami Ulus Research and Teaching Hospital

Obstetric and Gynecology Hospital and Radiology Department, Ankara, Turkey.

The uterine and spiral artery pulsatility and resistive indexes, systolic and diastolic ratios acceleration times and blood flow of both the right and left uterine artery were obtained by transvaginal color Doppler ultrasonography of consecutive viable pregnancies between 5 and 12 weeks gestation. Women were subsequently classified as having continuing pregnancies or pregnancy loss before 20 weeks gestation. To predict subsequent pregnancy loss, Doppler findings were adjusted for maternal age, history of previous abortion, presence of subchorionic hematoma, embryonic bradycardia, and gestational age by means of multivariate logistic regression analysis.

This was a prospective cohort study involving consecutive women with a first-trimester pregnancy underwent transvaginal ultrasonographic examination between February 2012 and December 2013. For the purposes of this study only the first scan that showed detectable fetal cardiac activity was considered for the study. Exclusion criteria included multiple pregnancy, ectopic pregnancy, missed abortion, and viable pregnancy before 5 weeks gestation with no detectable cardiac activity.

Miscarriage was defined as a fetal loss before 20 weeks gestation. Information about pregnancy outcome was obtained from the medical records or the referring obstetrician. Recorded variables the following demographic, ultrasonographic, and Doppler velocity parameters were recorded for each woman: 1) maternal age in years, 2) gestational age in completed weeks, 3) history of abortion (expressed as yes or no), 4) embryonic bradycardia (expressed as yes if the embryo had a heart rate lower than the fifth percentile for gestational age), 5) subchorionic hematoma (expressed as yes if an anechoic avascular perigestational image was visualised during the scan). Gestational age was adjusted according to the crown rump length at the time of the first-trimester scan.

All subjects were placed in a lithotomy position. The same investigator (BÖ) performed all sonographic examinations using a scanner (GE Logic S6, CA) equipped with spectral and color Doppler capability and a 12-MHz convex-array transducer. Assessment of pregnancy viability, fetal anomalies, and measurement of crown-rump length (CRL) were completed. The high-pass filter was set to the minimum, and the pulse repetition frequency was 2.5 kHz. The maximum achievable thermal and mechanical indices were 1.2 and 1.0, respectively, for Doppler sonographic examination. The size of the sampling gate was set to 2 mm. After visualisation of a midsagittal uterine section, the cervical canal was found. The probe was then moved laterally until the paracervical vascular plexus was demonstrated. Color Doppler was activated, and the uterine artery was identified as it turned cranially to make its ascent toward the uterine corpus. Spectral Doppler measurements of the uterine artery were recorded at this point before they branched into arcuate artery. Once it had been ensured that the insonation angle was < 30, the spectral Doppler gate was placed over the vessel. Angle correction was then applied, and the tracing was updated until at least three consecutive flow velocity wave-forms of satisfactory quality were displayed measurements from bilateral uterine artery included resistance index (RI), pulsatility index (PI), time-averaged mean velocity (in cm/sec), peak systolic velocity

**Table 1:** Clinical and ultrasonographic characteristics in the study group.

	Subsequent miscarriage (n = 25)	Continuing subsequent pregnancies* (n = 189)	Significance (P value)
Previous abortion + history-	11 (40%) 14 (56%)	18 (9.5%) 171 (90.5%)	0.016
Subchorionic + hematoma -	9 (36%) 16 (64%)	28(14.8%) 161(85.2%)	0.787
Embrionic+ bradycardia	6 (24%) 19 (76%)	24 (12.7%) 165 (87.3)	0.221
Maternal age	28.1 (19.4–38.9)	25.1 (18.0–39.1)	0.010
Gestational age	7.5 (5.9–10.3)	7.8 (5.6–11.2)	0.865
Uterine artery pulsatility index	2.0 (1.6–2.7)	2.0 (1.1–3.0)	0.686
Uterine artery resistance index	0.78 (0.67–0.89)	0.73 (0.65–0.87)	0.006
Uterine artery systolic /diastolic ratio	5.3 (4.6–6.7)	4.3 (3.5–6.1)	0.001
Uterine artery acceleration time (m/s2)	0.07 (0.05–0.14)	0.07 (0.04–0.14)	0.034
Uterine artery fetal blood low (ml/sn)	23.1 (20.4–28.0)	28.8 (21.0–37.0)	0.001
Spiral artery pulsatility index	2.0 (1.1–2.9)	1.8 (1.1–2.9)	0.320
Spiral artery resistance index	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.698
Spiral artery systolic/diastolic ratio	4.3 (3.9–6.3)	4.3 (3.5–6.7)	0.355
Spiral artery acceleration time (m/s2)	0.07 (0.04–0.14)	0.07 (0.04–0.14)	0.310
Spiral artery blood flow (ml/sn)	22.0 (19.0–27.0)	24.0 (19.5–28.1)	0.020

**Table 2:** Shows the values for the multiple regression analyses.

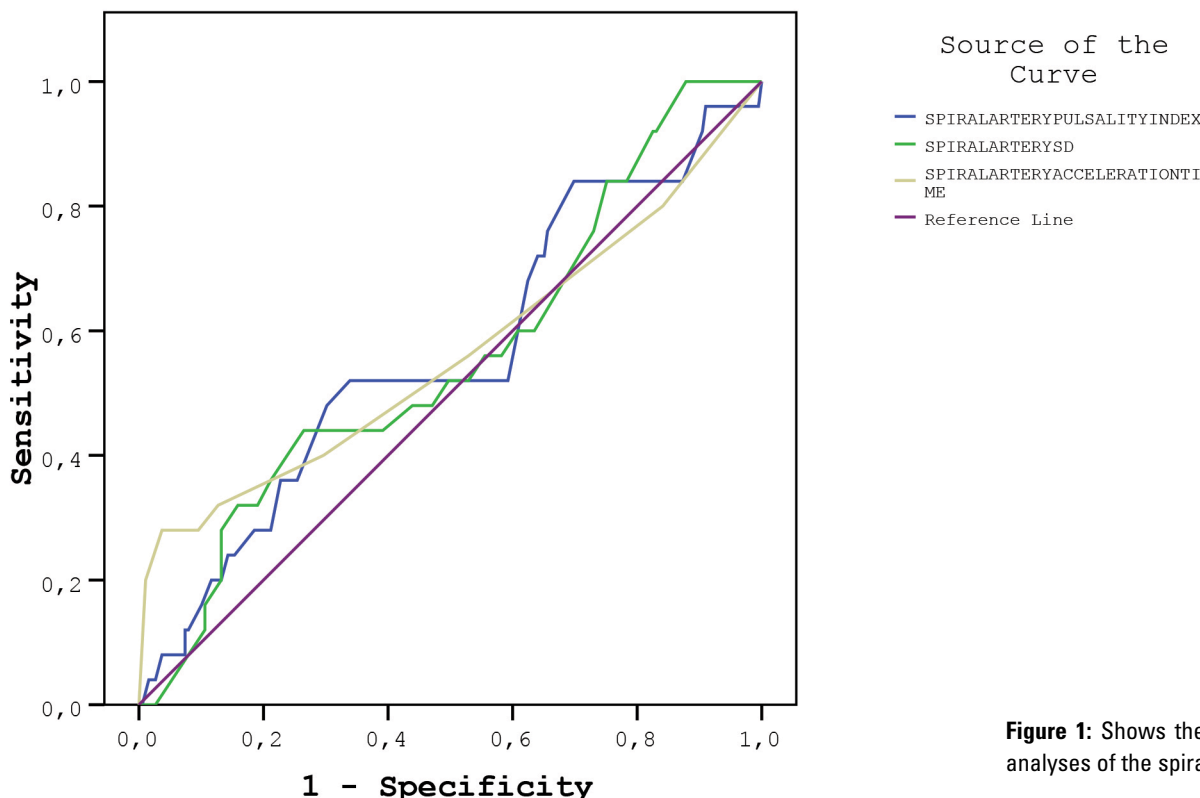
Parameters	Best cut-off	Specificity	Sensitivity	PPV	NPV	CI
Spiral artery pulsatility index	1.89	89	78	38	97	0.435–0.687
Spiral artery systolic /diastolic ratio	4.34	88	79	29	93	0.435–0.678
Uterine artery pulsatility index	2.03	88	84	27	91	0.417–0.633
Uterine artery Systolic/diastolic ratio	4.78	67	91	26	94	0.879–0.976

(in cm/sec), volume flow (in mL/min) and the presence or absence of a proto-diastolic notch. Arcuate artery was visualised at the external third of the myometrium with a characteristic blood flow pattern showing a moderate systolic velocity and an increased diastolic component. Radial artery was visualised in the myometrial tissue with a blood flow pattern characterised by a diastolic velocity which was half of its systolic velocity. Spiral artery was detected in the medial third of the myometrium. Doppler examinations were started at the lowest possible color-gain setting. The gain was gradually increased until a flow pattern was detected. Whenever flow was found, flow velocity waveforms were recorded. The spectral Doppler values were calculated from at least three successful satisfactory waveforms. The presence

or absence of an early diastolic notch was not included in the analysis. The pulsatility index, resistance index, uterine artery systolic/ diastolic value, acceleration time-averaged value and blood flow value of the right uterine and spiral artery were measured electronically once and recorded. The blood flow was measured automatically by the scanner (GE Logic S6, CA) after calculating the diameter of the artery.<sup>11,12</sup>

A multivariate analysis was performed by means of a regression model considering miscarriage before 20 weeks gestation as the dependent variable. Maternal age, previous abortion, sub chorionic hematoma, embryonic bradycardia, and gestational age were included in the regression model as independent variables. Doppler velocity parameters, such as

### ROC Curve



**Figure 1:** Shows the ROC CURVE for the analyses of the spiral artery values.

uterine artery and spiral artery pulsatility index, resistance index, uterine artery systolic/diastolic value, acceleration time-averaged value and blood flow value, were compared by receiver operating characteristic curves to select the variable with the largest area under the curve to be included in the multivariate logistic regression model. The SPSS for Windows 15 (SPSS, Inc., Chicago IL) were used for the statistical analyze.  $P < .05$  was considered statistically significant.

#### Results

There were 214 pregnancies with live embryos, 25 (11.7%) of which resulted in a miscarriage before 20 weeks gestation. None of the 214 women with pregnancy losses had a clinical history of cervical incompetence or hypertensive disease in the current pregnancy. Among these, 20 (80%) underwent a follow-up scan in our unit; four of these had a complete abortion and 16 of these had a missed abortion. Information from the latter group was used to determine the estimated gestational age at which fetal death occurred. The median gestational age at miscarriage, calculated from the crown-rump length of the dead fetus, was 7.5 weeks (range 5.6–11.2 weeks) and the median interval between the scan and fetal death was 1 week (range 0–5 weeks).

All pregnancies ending in miscarriage were scanned before 11.2 weeks gestation comparisons of recorded variables between women who miscarried and those who did not were therefore subsequently made for the 189 pregnancies in which the scan was performed between 6 and 8 weeks' gestation. As shown in Table 1, significant associations with miscarriage and previous abortion ( $P < .05$ ), embryonic bradycardia ( $P < .05$ ), maternal age, uterine

artery resistance index ( $P < .05$ ), systolic/diastolic ratio ( $P < .0001$ ), uterine artery acceleration time ( $P < .05$ ), uterine artery blood flow ( $P < .0001$ ) and spiral artery blood flow ( $P < .05$ ) were found in the bivariate analysis. No differences were noted between the groups in mean gestational age, presence of sub chorionic hematoma, uterine artery and spiral artery pulsatility index, resistance index, spiral artery systolic/diastolic value, and spiral artery acceleration time. As shown in Table 1, among Doppler velocity parameters studied the spiral artery and the uterine artery blood flow mL/s was lower in miscarriage group than the healthy carriage pregnancies (0.02, 0.01 respectively).

The resistance indexes in the spontaneous abortion group have not shown any statistical significant decrease before the 8th week. ( $P = 0.032$ )

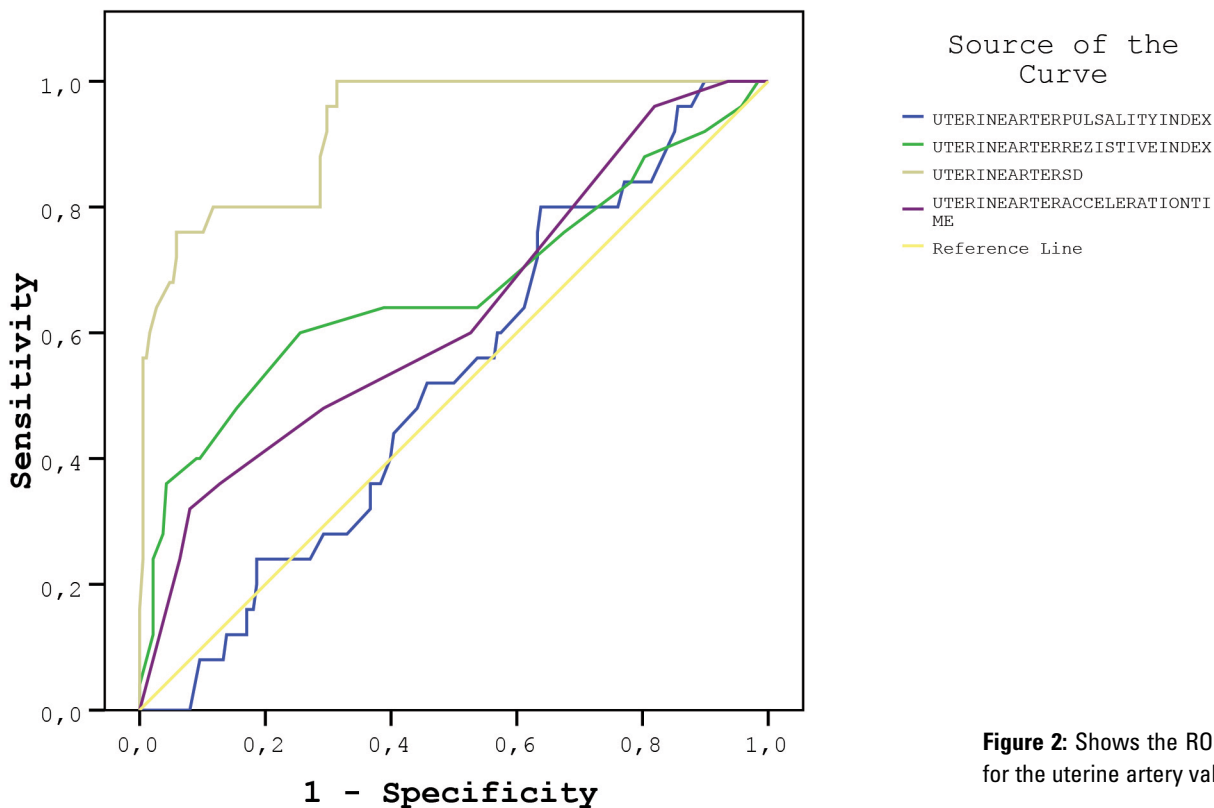
The area under the receiver operating characteristic curve for spiral artery pulsatility index is 0.561 ( $P = 0.064$ , 95% CI: 0.435–0.687). Table 2 shows the sensitivity and specificity rates for the Doppler indices.

Figure 1 and Figure 2 show the ROC for the Doppler indices.

#### Discussion

Early pregnancy loss is a common complication of pregnancy in first trimester pregnancy. The mechanisms are poorly understood in the evaluation of the uteroplacental circulation. Impairment of vascular remodeling in the maternal–fetal interface have been extensively associated with the pregnancy complications.<sup>18,19</sup> There is an agreement that there is a highly intensive vascular remodeling in early pregnancy which appears to be an important determinant of pregnancy outcome. The

### ROC Curve



**Figure 2:** Shows the ROC Curve analyses for the uterine artery values.

various branches of the uterine circulation can be differentiated by means of color and spectral Doppler imaging. The possibility of identifying the uteroplacental vascular alterations from the implantation process to the end of the pregnancy could provide a perfect diagnostic tool for the clinical management of the early pregnancies and its complications.<sup>20,21</sup>

In this study, blood flow analyses was performed on the uterine and spiral artery because first trimester uterine artery values are accepted as the to be one of the successful factors to predict the outcomes of the placental implantation of which is necessary for the continuous of the pregnancy. The small vessels such as the peritrophoblastic vessels or spiral artery are more to difficult to detect, but highly sophisticated equipment has been able to overcome this problem.<sup>22-25</sup> One of the benefits of this study is achieving the reproducibility of the results obtained from spiral artery spectral Doppler by means of mL/s by spectral artery Doppler.

There is a significant decrease of spiral artery resistance index after the 5th week of pregnancy which may reflect vascular remodeling in the maternal-fetal interface. This is because vascular remodeling by trophoblast invasion occurs at placentation, causing a reduction in local arterial resistance.<sup>26,27,28</sup> Our results show that the resistance to blood flow in the uterine artery and spiral artery each underwent different changes during early pregnancy. The present study showed cases of spontaneous abortion, with impaired growth of the gestational sac, whose UA-RIs remained high or failed to decrease normally between the 5th and 6th week of pregnancy. The high SA-RI between the 5th and 6th week of pregnancy may be a cause of spontaneous

abortion and reflect impaired vascular remodeling caused by failure of normal trophoblastic invasion at placentation. Although trophoblast invasion is limited to the endometrial part of spiral artery at the early stage of pregnancy. It is also reported that the blood flow from the RA nearest to the placental site would be the indicator of the histological changes taking place in the implantation site.<sup>19,29,30</sup> The decreased UA-RI at the placental site whereas SA-RI remains constant may reflect the local development of the shunts at the placental site such as between spiral artery and intervillous space, because a lower RI in the more distal part of the uteroplacental circulation indicates the development of such shunts. However, this suggests the possibility that the UA-RI was not affected because the change in UA-RI is a local event.<sup>11,31-33</sup> However, future studies are needed to determine the relationship between the Doppler spiral artery resistance and histological features of vascular remodeling.

There is substantial anatomical evidence that in the majority of cases the most common complications of the pregnancy stem from a defect in early trophoblast invasion and a failure to convert the spiral artery into low-resistance channels. Most studies described in the literature have shown that vascular resistance of the uteroplacental bed declines with advancing gestation. In our study vascular resistive indexes were higher in the subsequent miscarriage group than the continuing pregnancies. This finding is in agreement with other studies. However the resistive index values in these studies were between the 4th to the 16-18th week and showed that the demonstrable hemodynamic changes has occurred between the 14th week of the gestation. Pellizzari, *et al.* did not find any significantly change in the resistive index

although their study is between 6–12th gestational age.<sup>34</sup> In the subsequent miscarriage group the uterine artery and the spiral artery blood flow was lower than the control group. However in our study the gestational ages were similar to this study, in addition there was not a statistical significance in the spiral artery values, but in the uterine artery values. This results correlates with the anatomical findings because in the intervillous circulation the significant flow does not occur until the end of the first trimester, at approximately 10 weeks of gestation. This change in blood flow is intimately linked to the extravillous trophoblast migration, for during early pregnancy aggregates and an establishing free communications between the spiral artery and placenta is only established in these weeks.<sup>13–15</sup>

The intraplacental oxygen concentration increases from < 20 mm Hg at 10 weeks gestation to > 50 mmHg at 12 weeks with the onset of the maternal intervillous circulation.<sup>19,35</sup> This physiological burst of oxidative stress may play an important physiological role in triggering normal placental differentiation. There should be a gradient between the maternal and fetal tissues, which is essential as it influences cytotrophoblast proliferation and differentiation along the invasive pathway and promotes villous vasculogenesis.<sup>36,37</sup> As pregnancy advances between 7 and 16 weeks there is a progressive but independent increase in decidual pO<sub>2</sub>, which is most probably due to the increase in maternal blood flow volume.<sup>38</sup> There should be a hypoxic condition in the intervillous space before the 10th week, and vascularisation and flow in the peripheral region. In the patient with a hypoxic condition vascular spasm is expected, as is the expectation of increased values of gradient measurements. In vivo and physiological studies support that if there is an increased vascular tone, there is an increased resistance. With the Doppler findings this results with uterine arterial high pulsatility index values.<sup>39–42</sup> Among these results the most promising with adverse outcome Doppler value is uterine artery systolic/diastolic ratio. There are changes between the groups of miscarriage and continuing pregnancies about the spiral artery indices, but these values do not reach as a statistically significant value. This could be due to the gestational age in which the study was done. Second, the vascular alterations due to an abnormal placentation are present from the beginning of pregnancy but they are detectable only in the second trimester.<sup>8,43–45</sup>

On the other hand, this result also suggests that spiral artery blood flow analyses do not identify hemodynamic alterations which occur in abnormal pregnancy. Most likely the vascular changes which compromise the uteroplacental circulation in the first trimester are too small and too localised to influence to predict. Thus, physiologically in the first trimester nearly all of the vascular alterations have occurred in the uterine artery vascular bed and represent the sum of all changes. This could explain the uterine artery systolic /diastolic ratio to be the most promising predictive value for the subsequent miscarriage.

This prospective study has some limitations. First of all, this study was done in a single centre and needs to be confirmed with larger cohort groups. Second, a longitudinal assessment of the uterine and spiral artery could be repeated in order to understand the exact blood flow cut-off values for the continuous of the successful pregnancies.

In conclusion, this study confirms the important role of color

and spectral Doppler in understanding the vascular alterations in the uterine artery and spiral artery with correspondence to the pathophysiology of the uteroplacental circulation. The altered change of spiral artery may give a new insight into understanding the early stages of the pathophysiology of spontaneous abortion, such as at the first weeks of pregnancy after implantation. However, further studies are needed with larger sample sizes.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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