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Comparison of Superb Microvascular Imaging and Conventional Doppler Imaging Techniques for Evaluating Placental Microcirculation: A Prospective Study

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Background: Superb microvascular imaging (SMI) is a new blood flow imaging technique used to evaluate microvascular blood flow. This study evaluated whether SMI was superior to color Doppler flow imaging (CDFI) for evaluating placental microcirculation.

Material/Methods: This prospective study included pregnant women in their third trimester who were evaluated at General Hospital of Hebei Province from February to June 2017. The distribution of vascular patterns, including pulsatility index (PI), resistance index (RI), S/D, time average velocity (TAV), and vessels per unit area, were evaluated by SMI and CDFI.





Results: This study evaluated 110 pregnant women of mean age 29.53 years. SMI and CDFI yielded statistically significant differences in PI (0.76 vs. 0.62), RI (0.71 vs. 0.47), S/D (2.23 vs. 1.71), TAV (14.35 vs. 22.45), and vessels per unit area (0.26 vs. 0.05) ($P < 0.001$ each). The weight of the pregnant women correlated positively with RI ($P = 0.048$) and negatively with vessels per unit area ($P = 0.040$) as determined by SMI. Weeks of gestation correlated negatively with PI ($P = 0.008$), RI ($P = 0.004$), S/D ($P = 0.015$), and vessels per unit area ($P = 0.014$) by CDFI, and positively with RI ($P < 0.001$) and S/D ($P = 0.001$) by SMI. The results of stratified comparisons of CDFI and SMI based on age, weight, and gestational weeks were consistent overall.

Conclusions: SMI, which has a higher rate of placental vascularity, a clearer display of capillaries, a greater sensitivity to low flow, and an advantage in displaying microcirculation of the placenta, can serve as a new and effective method of evaluating placental blood flow.

MeSH Keywords: Hemodynamics • Placental Circulation • Ultrasonography, Doppler, Color

Abbreviations: SMI – superb microvascular imaging; CDFI – color Doppler flow imaging; PI – pulsatility index; RI – resistance index; TAV – time average velocity; CEUS – contrast-enhanced ultrasonography

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Background

Changes in maternal hemodynamics occur frequently during pregnancy, and blood perfusion of the uterus and placenta can affect the growth and development of the fetus [1]. Obstacles to uteroplacental microcirculation and reduced placental blood flow have been associated with risks of preeclampsia, fetal growth restriction, fetal distress, and other pathologies of pregnancy [1,2]. Careful monitoring of the placental microcirculation is therefore required to reduce adverse outcomes.

Placental vascularity can be assessed using several ultrasonic imaging techniques, including color Doppler flow imaging (CDFI), contrast-enhanced ultrasonography (CEUS), 3-dimensional power Doppler ultrasound (3D PD-US), and superb microvascular imaging (SMI). Although its ability to evaluate microvessels is limited [3], conventional CDFI has been used to monitor the perfusion of tissue. Specifically, CDFI provides information about macro-blood flow but does not provide any particulars. CDFI evaluates tissue perfusion by measuring the velocity of flow and computing indices, but CDFI cannot differentiate between actual low-velocity flow and movement artifacts [4,5]. CEUS improves the resolution of ultrasound by enhancing the backscatter echo based on the detection of gas-filled microbubbles, which are used to visualize microcirculation that is usually invisible by CDFI [6]. Because no study to date has shown that contrast agents are safe, the use of CEUS in pregnant women is limited. Although 3D PD-US can potentially overcome the shortcomings of CDFI and CEUS in assessing placental vascularity and blood flow by monitoring real-time, *in vivo* placental function [7–9], 3D PD-US is affected by patient or sonographer movements, therefore requiring it be performed during periods of fetal inactivity, and that the pregnant woman hold her breath [10].

SMI is a new blood flow imaging technique that uses a unique algorithm to minimize motion artifacts by eliminating signals based on an analysis of tissue movement [11]. This technique has been used to evaluate microvascular blood flow of the breasts and reproductive glands [12–14]. To date, however, no study has assessed the ability of SMI to evaluate placental microcirculation in pregnant women during their third trimester. The present study therefore compared the ability of CDFI and SMI to assess placental vascularity and number of blood vessels per unit area (n/cm^2), and to measure hemodynamic parameters of micro-blood vessels in pregnant women during their third trimester.

Material and Methods

Patients

This study recruited 110 healthy pregnant women aged 20–42 years without complications of pregnancy who were seen

at Hebei General Hospital during their third trimester (29–40 weeks) from February to June 2017. All recruited women had singleton pregnancies, and the development of the fetus was consistent with gestational age. Patients were excluded if they experienced premature rupture of fetal membranes, an abnormal fetal structure, or an abnormal placenta. The study protocol was approved by the Ethics Committee of Hebei General Hospital (Approval Number: 2018KYLS169), and all recruited women provided written informed consent.

Ultrasonographic examination

All ultrasound examinations, including CDFI and SMI, were performed with a curved transducer (6C1 Aplio500; Toshiba Medical Systems Corporation, Tochigi, Japan). When the fetus was in a relatively calm state, the participant was instructed to lie in the supine position. If the images were blurry, the participant was asked to hold her breath during acquisition. Following detection of the placenta by B-mode ultrasonography, the transducer was switched to the CDFI mode, and the appropriate sampling box was selected and adjusted to include placental tissue. The size of the sample may not have been exactly the same as the distribution of blood supply to the placenta, but the area of the sampling frame in the CDFI and SMI modes was the same. The flow gain was adjusted until the appropriate degree was reached, without any interference by color blood flow signals or noise, such as color flow spillover. The color velocity scale was adjusted to <5 cm/s, and the wall filter was adjusted to within 50–100 Hz. Settings for SMI included a color velocity scale of 1.0–2.0 cm/s and a frame rate >50 Hz. Gain settings were optimized for each image. When the image clearly showed the central vascular placenta previa, 2 physicians, each with >5 years of experience in obstetric ultrasonography and 12 months of experience in SMI, saved the image, recorded the sampling frame area (cm^2), and independently counted the number of vessels in the sampling frame area. The counting method began by excluding the vascular display at the edge of the placenta close to the mother and the large vascular display of the umbilical artery insertion site close to the fetus. Each physician counted the vascular display of the central placenta in the sampling box; the branched vascular trunk was counted separately, as were the vascular branches and microvascular displays. The average of the 2 physicians' counts was used in the analysis (n), and the numbers of vessels per unit area (n/cm^2) was calculated. The smallest artery was positioned in the center of the placenta and, while maintaining the angle between the ultrasound beam and blood flow at 0–60°, freeze frames of 3 to 5 clear and stable Doppler spectra were obtained. The pulsatility index (PI), resistance index (RI), and time average velocity (TAV, time) were automatically calculated using the software of the instrument. Once the view was stabilized, the instrument was switched to SMI mode and the same method was

Table 1. Placental microcirculation indexes between CDFI and SMI.

Variable	CDFI (n=110)	SMI (n=110)	Statistic	P value
PI (median, Q1 and Q3)	0.62 (0.43, 0.75)	0.76 (0.64, 0.89)	-1792.50	<0.001
RI (median, Q1 and Q3)	0.47 (0.40, 0.53)	0.71 (0.52, 0.89)	-2325.50	<0.001
S/D (median, Q1 and Q3)	1.71 (1.47, 2.05)	2.23 (1.99, 2.53)	-2129.00	<0.001
TAV (cm/s) (median, Q1 and Q3)	22.45 (17.20, 28.60)	14.35 (12.20, 16.80)	2793.50	<0.001
Count per unit area of vessel counts (cm ²) (median, Q1 and Q3)	0.05 (0.02, 0.08)	0.26 (0.19, 0.35)	-3052.50	<0.001

* Wilxon signed rank sum test.

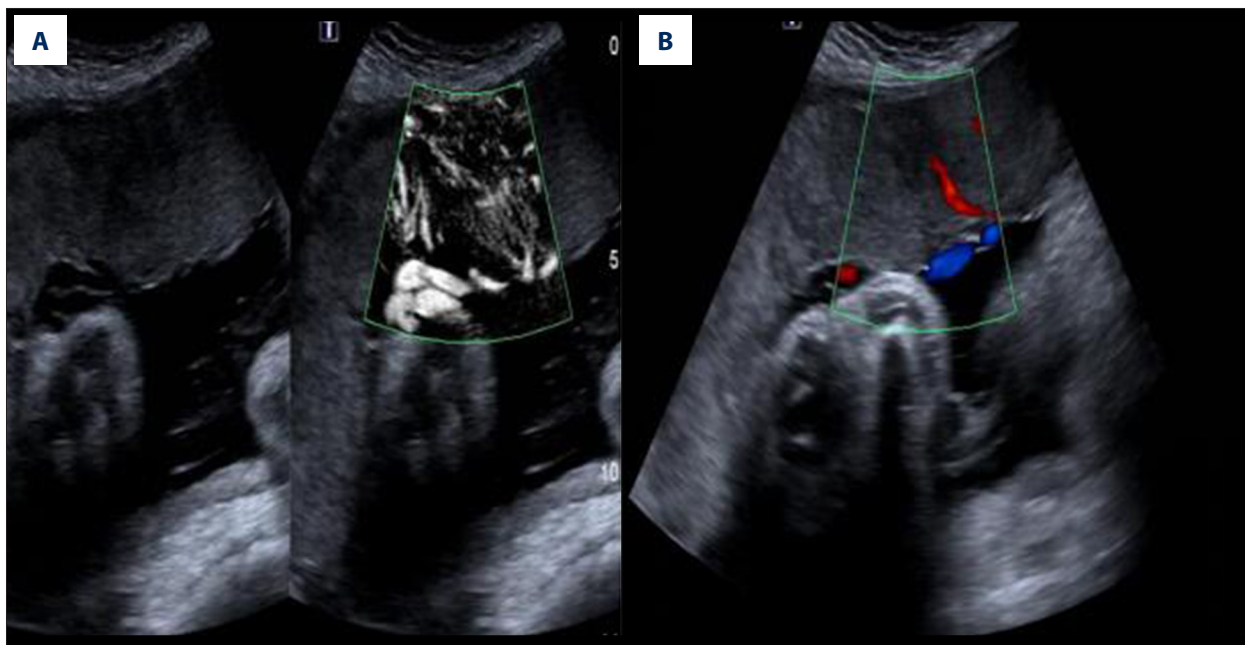


Figure 1. Vascular display of the central part of the placenta by (A) SMI and (B) CDFI of women after 30 weeks of gestation.

used to determine the relevant indicators. The position and size of the sampling box were consistent in SMI and CDFI, and all tests were performed by the same researcher used the same machine.

Statistical analysis

Data of CDFI and SMI from the same placenta sampling area were collected for statistical analysis. Normally distributed continuous parameters were expressed as the mean and standard deviation and compared by paired *t* tests. Non-normally distributed continuous parameters were expressed as the median and interquartile range (IQR) and compared using the Wilcoxon signed rank-sum test. Spearman rank correlation analyses were performed to calculate the relationships of age, weight, and weeks of gestation weeks with PI, RI, S/D, TAV, and number of vessels per unit area determined by CDFI and SMI modes.

Stratified analyses of the differences in placental microcirculation indices determined by CDFI and SMI were performed based on age, weight, and weeks of gestation. The agreements and biases between paired measurements by 1 and by 2 operators were determined by Bland-Altman analysis [15]. All tests were 2-tailed, with a level of significance of 0.05. All statistical analyses were performed using SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA).

Results

This study recruited 110 pregnant women, of mean age 29.53 years (range, 20.00–42.00 years) and mean weight 70.78 kg (range, 52.00–98.00 kg). All women were in their third trimester, with mean gestational age 34.42 weeks (range, 29.00–40.70 weeks). Table 1 shows vascular and arterial hemodynamic

Table 2. The correlation between age, weight, or gestational week and placental microcirculation indexes undergoing CDFI and SMI.

Parameters	Age		Weight		Gestational week	
	r	P value	r	P value	r	P value
CDFI: PI	-0.12	0.221	-0.04	0.689	-0.25	0.008
CDFI: RI	-0.11	0.246	0.02	0.812	-0.28	0.004
CDFI: S/D	-0.16	0.103	-0.02	0.845	-0.23	0.015
CDFI: TAV	0.01	0.940	-0.03	0.731	0.12	0.203
CDFI: Count per unit area of vessel counts	-0.01	0.904	-0.13	0.167	-0.23	0.014
SMI: PI	-0.04	0.690	0.06	0.570	0.05	0.620
SMI: RI	0.06	0.542	0.19	0.048	0.40	<0.001
SMI: S/D	-0.03	0.736	0.10	0.293	0.31	0.001
SMI: TAV	0.08	0.383	-0.19	0.051	-0.06	0.501
SMI: Count per unit area of vessel counts	-0.09	0.342	-0.20	0.040	-0.02	0.835

* Spearman rank correlation.

parameters of the placenta, as determined by CDFI and SMI. SMI detected significantly greater numbers of blood flow signals than CDFI for all pregnant women with placental display, with the mean numbers of blood vessels per unit area being significantly greater for SMI than for CDFI (0.26/cm² vs. 0.05/cm², $P<0.001$). SMI yielded significantly higher values than CDFI for the PI (0.76 vs. 0.62, $P<0.001$) and RI (0.71 vs. 0.47, $P<0.001$) of the smallest bed artery, as well as for S/D (2.23 vs. 1.71, $P<0.001$), and a significantly lower value for TAV (14.35 vs. 22.45, $P<0.001$).

Figure 1 shows the vascular display of the central part of the placenta using the 2 ultrasound modalities. CDFI and SMI images of blood flow through the same slice of the placenta were similar. However, the CDFI mode showed only a few thick blood vessels, whereas the SMI mode showed more blood vessels and more branched vessels than CDFI. Regardless of color or monochrome mode, the number of blood vessels with microvascular shapes and contours were more pronounced and more sensitive to SMI than to CDFI.

Table 2 shows the correlations of subject age, weight, and gestational weeks with PI, RI, S/D, TAV, and number of vessels per unit area on CDFI and SMI. Overall, age did not correlate significantly with PI, RI, S/D, TAV, and number of vessels per unit area on either CDFI or SMI ($P>0.05$). Weight showed a significant positive correlation with RI ($r=0.19$, $P=0.048$) and a significant negative correlation with number of vessels per unit area ($r=-0.20$; $P=0.040$) on SMI but not CDFI. Number of weeks of gestation was negatively correlated with PI ($r=-0.25$; $P=0.008$), RI ($r=-0.28$; $P=0.004$), S/D ($r=-0.23$; $P=0.015$), and number of vessels per unit area ($r=-0.23$; $P=0.014$) on CDFI. In contrast, number of weeks of gestation was positively correlated with RI ($r=0.40$; $P<0.001$) and S/D ($r=0.31$; $P=0.001$) on SMI. These

differences between CDFI and SMI remained statistically significant following stratification of PI, RI, S/D, TAV, and number of blood vessels per unit area by age, weight, and weeks of gestation (Table 3).

Figure 2 shows the results of intraobserver and interobserver agreements for the same stored images obtained by CDFI and SMI modes. None of the 95% confidence intervals exceeded the limits of consistency, with the 2 evaluators showing consistent results for both the CDFI and SMI modes.

Discussion

The placenta is the intermediary organ between the mother and the fetus, enabling the exchange of maternal and fetal material. Placental function can affect fetal growth status directly, as well as blood perfusion and fetal safety. During normal pregnancies, uteroplacental blood flow increases with gestational age. Placental circulation is characterized by low-velocity blood flow and root-like branching. After penetrating the chorionic plate, the umbilical vessels divide into primary stem villi, secondary stem villi (branches of the primary stem villi), tertiary stem villi (branches of the secondary stem villi), cotyledon vessels, and branches of small villous vessels [16]. The current study compared the number of blood vessels and hemodynamics detected by CDFI and SMI modes in pregnant women during the third trimester. PI, RI, S/D, and number of blood vessels per unit area were found to be significantly higher, and TAV significantly lower, on SMI than on CDFI. Although weight and gestational age correlated significantly with several placental microcirculation indices, the results of stratified analyses based on pre-defined factors were consistent overall.

Table 3. subgroup analyses for placental microcirculation indexes between CDFI and SMI.

Variable	Factors	Group	CDFI (n=110)	SMI (n=110)	Statistic	P value
PI	Age (years)	≥30 (n=48)	0.58 (0.44, 0.70)	0.76 (0.65, 0.83)	-409.50	<0.001
		<30 (n=62)	0.64 (0.42, 0.77)	0.76 (0.63, 0.92)	-493.50	<0.001
	Weight (Kg)	≥70 (n=59)	0.58 (0.42, 0.75)	0.79 (0.67, 0.92)	-590.50	<0.001
		<70 (n=51)	0.64 (0.48, 0.76)	0.75 (0.61, 0.87)	-312.00	0.002
	Gestational week	≥36* (n=41)	0.54 (0.43, 0.64)	0.79 (0.67, 0.91)	-7.17	<0.001
		<36 (n=69)	0.68 (0.48, 0.83)	0.75 (0.63, 0.89)	-464.00	0.004
RI	Age (years)	≥30 (n=48)	0.46 (0.38, 0.50)	0.71 (0.52, 0.90)	-462.50	<0.001
		<30 (n=62)	0.48 (0.42, 0.54)	0.71 (0.54, 0.89)	-717.00	<0.001
	Weight (Kg)	≥70 (n=59)	0.46 (0.39, 0.53)	0.78 (0.39, 0.53)	-700.00	<0.001
		<70 (n=51)	0.48 (0.41, 0.52)	0.59 (0.51, 0.85)	-465.50	<0.001
	Gestational week	≥36 (n=41)	0.44 (0.38, 0.47)	0.87 (0.74, 0.94)	-392.50	<0.001
		<36 (n=69)	0.48 (0.44, 0.54)	0.57 (0.50, 0.78)	-726.00	<0.001
S/D	Age (years)	≥30 (n=48)	1.64 (1.44, 1.93)	2.23 (1.99, 2.46)	-441.50	<0.001
		<30 (n=62)	1.77 (1.49, 2.10)	2.24 (2.00, 2.67)	-637.00	<0.001
	Weight (Kg)	≥70 (n=59)	1.67 (1.47, 2.08)	2.32 (2.00, 2.67)	-650.50	<0.001
		<70 (n=51)	1.78 (1.47, 2.05)	2.20 (1.94, 2.45)	-420.00	<0.001
	Gestational week	≥36 (n=41)	1.59 (1.47, 1.76)	2.41 (2.17, 2.67)	-354.50	<0.001
		<36 (n=69)	1.86 (1.48, 2.11)	2.10 (1.94, 2.43)	-673.50	<0.001
TAV (cm/s)	Age (years)	≥30* (n=48)	22.10 (15.45, 28.80)	14.25 (12.70, 16.70)	7.63	<0.001
		<30 (n=62)	22.85 (18.20, 28.60)	14.45 (11.30, 16.90)	897.50	<0.001
	Weight (Kg)	≥70 (n=59)	23.10 (17.40, 27.40)	13.70 (11.70, 15.50)	805.00	<0.001
		<70* (n=51)	22.30 (16.50, 30.10)	14.60 (12.30, 17.30)	7.94	<0.001
	Gestational week	≥36 (n=41)	23.70 (19.50, 28.60)	13.40 (11.50, 15.30)	420.50	<0.001
		<36 (n=69)	21.50 (16.20, 28.60)	14.60 (12.30, 17.20)	1055.50	<0.001
Count per unit area of vessel counts (cm ²)	Age (years)	≥30 (n=48)	0.05 (0.02, 0.09)	0.25 (0.20, 0.34)	-588.00	<0.001
		<30 (n=62)	0.05 (0.02, 0.08)	0.28 (0.17, 0.35)	-976.50	<0.001
	Weight (Kg)	≥70 (n=59)	0.04 (0.02, 0.08)	0.25 (0.17, 0.33)	-885.00	<0.001
		<70 (n=51)	0.05 (0.03, 0.09)	0.28 (0.22, 0.38)	-663.00	<0.001
	Gestational week	≥36* (n=41)	0.03 (0.02, 0.05)	0.26 (0.20, 0.34)	-14.27	<0.001
		<36 (n=69)	0.05 (0.03, 0.10)	0.26 (0.19, 0.36)	-1207.50	<0.001

The finding that TAV was significantly lower on SMI than on CDFI indicates that SMI is more sensitive to low blood flow. Both PI and RI are indicators of vascular compliance and the elastic state, which reflect the magnitude of blood flow resistance. The differences in PI and RI observed with SMI and CDFI may have been due to the application by CDFI of filtering techniques to eliminate noise and motion artifacts. Thus, CDFI can only detect large blood vessels with blood flow velocity above

the wall-filter threshold [17]. Therefore, low-velocity blood flow information is lost, and it is impossible to determine the shape of the blood vessels in the placenta. Additionally, morphological and experimental results showed that CDFI is not ideal for evaluating the placental microcirculation.

In contrast, SMI uses the high-end ultrasound diagnostic device architecture of the Aplio series to construct a high-density

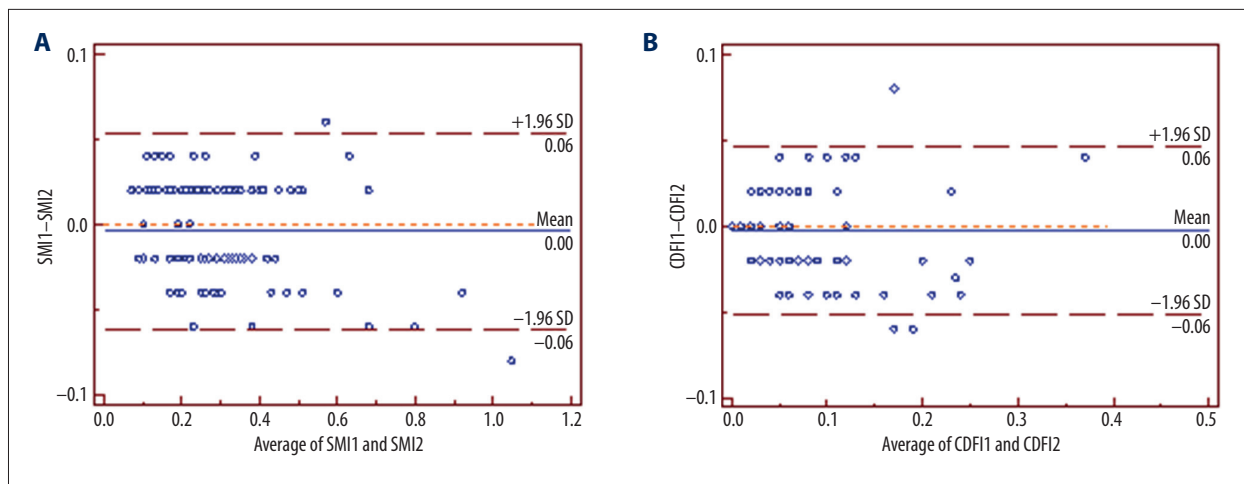


Figure 2. Number of blood vessels per unit area determined by (A) SMI and (B) CDFI modes, as calculated by the Bland-Altman method.

beamformer and a real-time application platform, enabling this mode to image low-velocity blood flow at a higher frame rate [4]. Frame rate imaging has high spatial resolution and minimal motion artifacts [18]. SMI uses an intelligent measurement and calculation system to distinguish tissue motion noise from real blood flow information, and displays low-velocity blood flow information through signal processing technology [19]. SMI has a significant advantage over CDFI in detecting smaller placental blood vessels and low-velocity blood flow. The present results confirm that the SMI model can better reflect microcirculation of the placenta, which is of great significance for the assessment of placental blood flow during pregnancy.

This study found that weight was positively correlated with RI and negatively correlated with the number of blood vessels per unit area measured by SMI. The development of the placental villous vasculature is regulated by vascular endothelial growth factor (VEGF), with the response to VEGF in syncytiotrophoblasts of the placenta reduced in obese women [20]. Moreover, weeks of gestation, which correlates significantly with placental development, was found to also correlate significantly with several indices in both the SMI and CDFI modes.

This study had several limitations, including the difficulty in visually distinguishing the level of villous stems. Moreover, no standards have yet been developed to evaluate placental pathology, thus preventing classification of the vessels shown. The results of our stratified analyses should be interpreted cautiously owing to potential multiple comparisons. Factors such as maternal abdominal wall thickness, fetal movement, and sampling position will affect the detection ability of SMI. Studies are needed that focus on assessments of placental pathology and other ultrasound indicators during pregnancy,

as well as the association between these indicators and fetal prognosis. Although additional studies are needed to assess the ability of SMI to evaluate placental microcirculation, the results presented in the present study indicate that this new blood flow imaging technique is acceptable for use during perinatal clinical assessments.

Conclusions

PI, RI, S/D, and number of blood vessels per unit area were significantly higher, and TAV significantly lower, when assessed by SMI mode than by CDFI mode in pregnant women during the third trimester. Doppler ultrasound SMI technology is simple and reproducible and provides a clearer microvascular display than CDFI. Moreover, SMI is associated with a higher rate of placental vascular manifestations and is more sensitive to low-velocity blood flow than CDFI, making it the most advanced technique to date for detecting the placental microcirculation. Although further study is needed to verify our findings, SMI has potential clinical value.

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Conflicts of interest

None.

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