OBSTETRICS

Effects of maternal cigarette smoking on placental volume and vascularization measured by 3-dimensional power Doppler ultrasonography at 11+0 to 13+6 weeks of gestation

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OBJECTIVE: We sought to establish the effect of maternal smoking on placental volume and vascularization in early gestation.

STUDY DESIGN: Three-dimensional power Doppler ultrasonography of the placenta was performed at 11+0 to 13+6 weeks in 80 pregnancies categorized according to cigarette consumption: group A never smoked, B smoking < 10 cigarettes/day, C smoking 10-20 cigarettes/day, and D smoking > 20 cigarettes/day. Using a standardized setting, placental volume and vascularization index (VI), flow index (FI), and vascularization flow index (VFI) were calculated.

RESULTS: No differences were found in placental volume among groups. In groups C and D lower values were found for VI (group C: t = 4.52, $P = .0002$; group D: t = 3.72, $P = .0014$), FI (group C: t = 5.06, $P = .0001$; group D: t = 4.59, $P = .0002$), and VFI (group C: t = 3.49, $P = .0024$; group D: t = 2.88, $P = .0095$). Placental vascular indices were significantly related to birthweight (VI r = 0.563, FI r = 0.580, VFI r = 0.601; $P < .001$).

CONCLUSION: Maternal smoking is associated with altered 3-dimensional placental Doppler indices and these changes are related to birth weight.

Key words: maternal smoking, placenta vascularization, placental volume, 3-dimensional ultrasound

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Although the profound effects of maternal smoking on birth size are well established,[1-4] little is known about the underlying mechanisms constraining fetal growth.[5] Morphological studies indicate that smoke produces a direct effect on placental development with a decrease in its vascularization.[6] However, Doppler studies of uterine and umbilical circulations have not allowed validating this hypothesis. This may be due to the limitations of these studies evaluating indirectly placental circulation by studying umbilical or uterine circulations.[7-9] Recent advances in ultrasound allow the combination of 3-dimensional (3D) ultrasound with power Doppler making it possible to quantify Doppler signals in a volume obtained by 3D scanning thus allowing to assess the whole placental circulation.[10-12] To test the hypothesis that maternal smoking may induce detectable changes in placental size and circulation, we applied this new technique to the analysis of placental volume and 3D vascularization at 11+0 to 13+6 weeks of gestation and we relate these results to maternal smoking status.

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Materials and Methods

After obtaining written informed consent from the mothers, we routinely performed in our fetal medicine center placental volume and vascularization assessment in pregnancies undergoing 11+0 to 13+6 weeks' ultrasonographic examinations as part of a prospective project on placental development approved by our local review board. This gestational age interval was selected because at this time it is still possible to obtain easily placental volume and vascularization whereas with increasing gestation the placental dimensions exceed the size of the volume box and thus it is not possible to record the whole placental volume.

From our database we retrospectively selected 80 pregnancies categorized according to their cigarette consumption as: never smoked (group A, n = 20), smoking < 10 cigarettes/day (group B, n = 20), smoking 10-20 cigarettes/day (group C, n = 20), and smoking > 20 cigarettes/day (group D, n = 20). Furthermore, no women of group A smoked before pregnancy and all women of groups B, C, and D started to smoke at least 2 years before pregnancy and did not reduce or quit their smoking habits during pregnancy. Further inclusion criteria were: (1) singleton pregnancies; (2) successful recordings of placental volume and 3D vascularization; (3) absence of preexisting maternal diseases (eg, dia-

TABLE 1
Clinical characteristics of pregnancies studied

	Group A (n = 20) Nonsmokers	Group B (n = 20) 0-10 cigarettes/day	Group C (n = 20) 10-20 cigarettes/day	Group D (n = 20) > 20 cigarettes/day
Age (y)	30.8 ± 4.9	31.3 ± 5.2	30.7 ± 5.4	29.8 ± 5.4
Weight (kg)	64.6 ± 9.5	62.7 ± 9.3	65.3 ± 11.4	62.6 ± 10.4
BMI (kg/m^2)	23.8 ± 4.1	23.6 ± 3.9	23.5 ± 4.0	23.4 ± 4.7
Gestational age at ultrasound (wk)	12.4 ± 0.8	12.6 ± 0.7	12.7 ±. 0.8	12.6 ± 0.7
Gestational age at delivery (wk)	39.9 ± 1.2	39.1 ± 1.7	39.3 ± 1.9	38.8 ± 1.9
Birthweight (g)	3230 ± 280	3249 ± 304	2899 ± 480[a]	2790 ± 432[b]
Birthweight *z* score	0.02 ± 0.70	0.41 ± 1.44	–0.80 ± 1.52[c]	–1.06 ± 1.22[d]

BMI, body mass index.
Data are expressed as means ± SD.
[a] Versus group A: t = 2.66, $P = .0113$; [b] Versus group A: t = 3.82, $P = .0005$; [c] 1-Sample *t* test: t = 2.35, $P = .0295$; [d] 1-Sample *t* test: t = 3.81, $P = .001$.

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betes, chronic hypertension, renal disease); (4) absence of fetal structural or chromosomal anomalies; and (5) exhaustive follow-up (ie, delivered in our department, allowing confirmation of smoking habits and occurrence of maternal and fetal complications). A priori analysis demonstrated that the sample size was sufficient to achieve a power of 90% with an α value of 0.05 for all the vascular indices tested.

An ultrasound machine (Voluson 730; GE Healthcare Kretztechnik, Zipf, Austria) with a 4- to 8-MHz transducer was used for 3D volume scanning using previously reported technique.[13,14] Using the same preestablished instrument settings in all the cases (angio mode: cent; smooth: 4/5; FRQ: low; quality: 16; density: 6; enhance: 16; balance: G>150; filter: 2; actual power: 2 dB; pulse repetition frequency: 0.9 kHz), power Doppler was applied to image the placental vasculature. The 3D placental volume was acquired keeping the probe perpendicular to the placental plate and the size of volume box size was adapted to fully include the placenta. The sweep angle was set at 85 degrees. The placental volumes were stored and later analyzed offline by an observer blinded of the smoking status. Software (Virtual Organ Computer-aided AnaLysis [VOCAL] II; GE Medical Systems, Milwaukee, WI) was used to evaluate placental volume. The contour mode in the software program (VOCAL II; GE Medical Systems) was set to manual. The rotation steps were set at 15 degrees[14] and 12 contours of the placenta were drawn manually after a 15-degree rotation from the previous 1 as automatically performed by the software. Once all contours had been drawn, the volume of the cervix was automatically calculated.

After estimation of the placental volume, the 3D power Doppler histogram was used to determine vascular indices from computer algorithms.[14] The vascular indices analyzed were: (1) the vascularization index (VI), which refers to the color voxel/total voxel ratio (ie, the color percentage within the volume of interest [placenta]) and provides an indication of how many vessels can be detected within the placenta (vascularity); (2) the flow index (FI), which refers to the weighted color voxel (on a scale of 0-100)/total color voxel ratio and provides an amplitude value for the color signal, thus giving informations on how many blood cells are transported at the time of the 3D sweep (placental blood flow); and (3) the vascularization-flow index (VFI), which refers to the weighted color voxel/total voxel ratio, combining the informations on vessel presence (vascularity) and amount of blood cells transported (blood flow).[15]

The Shapiro-Wilk test was used to analyze the normal distribution of the data. Because all the ultrasonographic parameters considered change with increasing fetal crown-rump length, data were expressed as the number of SD (*z* score) from which they differ from the expected mean difference obtained from previously constructed reference limits.[14,15] Similarly, birth weights were expressed as *z* score calculated from Italian population standards after correction for gestational age and sex of the newborn.[16] The 1-sample *t* test was used to evaluate significant differences. Comparison between continuous and categorical variables was performed by unpaired *t* test and Fisher's exact test, respectively. Relationships between the ultrasonographic parameters and birth weight *z* score were estimated by Pearson correlation coefficient. A P value $< .05$ was considered as significant.

RESULTS

The characteristics of the pregnancies studied are reported in Table 1. There were no differences among groups concerning their general characteristics. Birthweight was significantly lower in newborns of groups C and D when compared with group A, whereas no differences were evidenced between groups B and A. Similar findings were evidenced when birthweight *z* scores were considered. None of the patients included experienced bleeding during the second and third trimester. None of the preg-