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venous hemodynamics

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Abstract

Objective

To relate Doppler velocimetry findings in fetoplacental and uteroplacental circulation to placental histomorphology.

Material and Methods

In 14 uncomplicated and 31 high-risk pregnancies Doppler velocimetry was performed in umbilical artery and vein, and in maternal uterine veins and arteries during the second half of gestation. Histopathology of the placentas was examined especially for signs of ischemia and inflammation.

Results

All fetuses in uncomplicated pregnancies had normal flow velocity waveforms in umbilical artery; in the high risk group 18 fetuses had abnormal flow (increased PI or absent/reverse end-diastolic flow). The latter group had more often high ischemic score and infarctions in the placenta than found in pregnancies with normal umbilical artery flow (p<0.001 and p=0.02, respectively). Similarly, the abnormal uterine artery flow pattern (uterine artery score 3-4) occurred more often with high ischemic score and placenta infarctions (p<0.001 and p<0.001, respectively). No significant associations were found between the uterine venous flow type and placental ischemia.

Conclusion

Placental ischemic morphological changes were associated with Doppler ultrasound signs of increased resistance to arterial blood flow both on the fetal and maternal sides of the placenta. No significant relation to the uterine venous flow velocities was found.

Introduction

A normal development of placenta in early pregnancy is dependent on an adequate

invasion of trophoblast cells into decidual and myometrial segments of spiral arteries.

Several studies have shown that deficient trophoblast invasion is associated with

increased placental vascular resistance in the fetoplacental and uteroplacental circulation

and development of preeclampsia and/or intrauterine growth restriction (IUGR) [1,2].

The increased resistance to flow in the umbilical and uterine arteries can be detected

with Doppler ultrasound that is used as a part of a clinical protocol in surveillance of

high risk pregnancies [3,4]. However, the results of Doppler velocimetry have not

always been predictive of placental pathology [5,6]. This is probably due to the fact,

that human placenta has vast compensatory capacity and/or that there are very few well-

designed studies correlating a comprehensive morphological placenta examinations to

antenatal hemodynamic findings obtained with Doppler ultrasound.

At the histopathological placenta examination in cases of placental abruption, we

observed signs of venous congestion on the maternal side of placenta. This raised the

question of potential clinical significance of an abnormal placental-maternal venous

return and likelihood that uteroplacental venous flow could facilitate the detection of

early changes in intraplacental circulation. Recently, we established the feasibility of

assessing uterine venous flow velocities and demonstrated that pulsating blood flow

velocity in uterine veins was associated with abnormal Doppler findings in the uterine

artery [7].

The aim of the present study was to relate the Doppler velocimetry findings in uterine

veins and arteries and in umbilical artery to placental morphology in uncomplicated and

high-risk pregnancies, respectively. In addition to conventional histopathological

examination of placenta, special attention was paid to the degree of ischemic pathology

and inflammatory infiltration of decidua basalis.

Material and Methods

The study comprised 45 singleton pregnancies; 14 of pregnancies were uncomplicated

and 31 were high-risk pregnancies. The demographic data and the outcome of

pregnancies are presented in Table I. The 14 uncomplicated pregnancies were recruited

at routine ultrasound examinations in the second half of gestation. The 31 high-risk

pregnancies were referred for Doppler examination of fetal and maternal circulation as a

part of clinical surveillance; 14 were referred because of suspected IUGR, 8 because of

preeclampsia and 5 patients had both preeclampsia and IUGR. In the remaining 4 cases,

the indication for Doppler velocimetry were pregnancy induced hypertension, premature

preterm rupture of membranes, hepatitis C, and diabetes mellitus, respectively.

The ultrasound examinations were performed transabdominally with a Philips HDI

5000 system using a 5-2 MHz transducer (Philips Medical Systems, Bothell, WA). All

examinations were done by one of the authors (AT) on women reclining in a standard

hospital bed. The Doppler signals were recorded during periods of fetal apnea and

quiescence, and during short voluntary maternal apnea. The blood velocity signals of

umbilical artery and vein were recorded from the free-floating part of the umbilical

cord. The Doppler signals from maternal uterine arteries were recorded from the sample

volume placed over the uterine artery just above its crossing with iliac vessels on both

sides of uterus. The uterine veins were identified close to the uterine artery using colour

Doppler as described previously [7].

Pulsatility index (PI) was calculated from at least ten uniform waveforms in the flow

velocity spectrum of umbilical artery and of both uterine arteries. The waveform

patterns in the umbilical artery were also described semiquantitatively according to

blood flow classes (BFC) [8]:. BFC normal, PI within normal limits of the reference [9]

and positive diastolic flow; BFC I, PI > mean +2SD and ≤ mean +3SD, and positive

diastolic flow; BFC II, PI > mean +3SD and positive diastolic flow; BFC IIIA, absent

end-diastolic flow velocity; BFC IIIB, reverse end-diastolic flow velocity. The flow in

the umbilical vein was considered normal if continuous non-pulsatile. The uterine artery

blood velocity spectrum was also evaluated semiquantitatively according to the uterine

artery score (UAS) [4]: UAS 0, PI within normal limits [10] and no early diastolic notch

in both uterine arteries; UAS 1-3, one up to three abnormal findings, i.e., either PI >1.20

or notch established visually; UAS 4, PI ≥1.20 and early diastolic notch bilaterally. The

uterine venous flow pattern was described in three flow velocity types [7]: type I,

continuous non-pulsatile flow; type II, pulsatile flow with a "notch" down to the zero

line; type III, pulsatile pattern with absent flow during a part of the heart cycle.

After delivery, the placentas were weighed and then left to drain at room temperature

for 4 to 6 h followed by fixation in 10 % formalin. The weight of the fixated placentas

was assessed after dissection of the umbilical cord, membranes and coagula, when

present. Tissue sampling for histological examination was based on a minimum of 6

paraffin blocks including 8 standard samples of tissue: umbilical cord (two); membrane

roll (one); umbilical cord insertion (one); cotyledons with normal appearance including

maternal lakes (two); decidua basalis (opening of spiral arteries) (two). In addition, a

variable number of samples from gross lesions were examined (up to 12 paraffin blocks

per placenta). Tissue samples were embedded in paraffin and stained with hematoxylin-

eosin.

All sections were examined by one of the authors (RL) and the findings were classified

for conventional pathology with special emphasis on occurrence of mural thrombosis,

hemorrhagic endovasculitis, avascular villi, sclerosing endarteritis, ischemia (increased

syncytial knotting), ischemic villitis (microinfarctions), infarctions, perivillous fibrin

deposition (focal or massive), villitis of unknown etiology, decidual (i.e.,

uteroplacental) vasculopathy (inadequate trophoblast infiltration, acute atherosis, and

thrombosis in decidual vessels). Fetoplacental thrombotic vasculopathy included mural

thrombosis, hemorrhagic endovasculitis, and avascular villi. The presence of

inflammatory cells (mostly lymphocytes and occasional plasma cells) in the decidua

basalis indicated chronic deciduitis that was quantified in four grades: grade D0 (no

cells), grade D1 (occasional cells), grade D2 (several foci with cells), grade D3 (diffuse

infiltration) (Fig 1).

The degree of ischemic pathology was defined using the recently described placenta

ischemic score (IS) [11]. The IS represents the sum of ischemic lesions (ischemia,

ischemic villitis, and infarction) observed on histological examination - one point for

the presence of each lesion in respective section, several similar lesions observed in the

same section being counted as one. An abnormal IS was defined as ≥ 1. In addition we

calculated an ischemic score index (ISI) - IS divided by the number of available sections

with parenchyma. The section from the insertion was considered only when represented
by a complete transplacental section.

The use of Doppler ultrasound in pregnancy was approved by the Regional Research
Ethics Committee and the women participated in the study after giving their informed
consent.

Mann-Whitney test and Fisher´s exact test were used for statistical analysis as
appropriate. MedCalc version 9.1.0.1. statistical package (MedCalc Software,
Mariakerke, Belgium) was used for calculations.

Results

The placenta weight was significantly higher in the group of uncomplicated pregnancies
than in the group of high-risk pregnancies (p<0.001) (Table II). Placenta infarctions and
high IS (2-9) were significantly more often found among high-risk pregnancies (p<0.01
and p<0.001, respectively) that also had higher median ISI (p<0.001). The distribution
of deciduitis grades was similar in both groups (p=0.07) (Table II).

In all uncomplicated pregnancies the blood velocity waveforms in umbilical artery were
normal (BFC normal) and the flow in umbilical vein was normal non-pulsatile. In the
high risk group, 13 patients had normal umbilical artery BFC, 2 had BFC I, 4 BFC II, 9
BFC IIIA, and 3 BFC IIIB. Two patients with BFC II and 6 with BFC III had pulsations
in the umbilical venous flow. The findings of high UAS were more common in the
group of high-risk pregnancies (two patients with UAS 1, three with UAS 2, four with

UAS 3, and 15 patients with UAS 4) than in the group with uncomplicated pregnancies

(UAS 1 in one and UAS 2 in two women).

The distribution of Doppler velocimetry findings according to the results of placenta

histomorphology in total material is presented in Table III. No statistically significant

differences were found between the various uterine venous flow types with regard to the

IS (p = 0.17), ISI (p = 0.21), presence of infarctions (p = 0.14) and degree of deciduitis

(p = 1.00)., Abnormal umbilical artery flow velocity waveforms (BFC I-III) were

significantly more often found in cases with infarctions or with high IS (p=0.02 and

p<0.001, respectively) than in cases without signs of placental ischemia. The median ISI

was higher in cases with BFC I-III than in those with BFC normal (p<0.001). Similar

differences were found for the uterine artery Doppler findings: there was association

between the high UAS (3-4) and infarctions (p<0.001), and between high UAS and high

IS (p<0.001). The median ISI was higher in cases with UAS 3-4 than in those with UAS

0-2 (p<0.001).

Discussion

In recent years, developments in Doppler ultrasound technology substantially improved

the possibilities to detect and visualize low velocity flows also in small vessels. The

sensitivity of colour Doppler has increased and it is now possible to find and record

Doppler flow signals of maternal veins including the uterine veins [7]. Previously, we

showed that abnormal flow velocity patterns in uterine veins (types II and III) were

associated with abnormal Doppler findings in the uterine artery (UAS 2-4) [7].

Therefore, we have expected to find an association between histomorphological findings indicating placenta ischemia and abnormal uterine venous blood flow type. However, the present findings failed to confirm it. There are limiting factors that might have at least partly contributed to this. The ultrasound method might still not be at the necessary technical level in order to detect discrete changes in the venous return from placenta that includes a very special vascular anatomy comprising both chorio-decidual sinuses and draining uterine veins [12]. Another factor might be the size and composition of the present clinical material.

In agreement with our previous studies [11,13], we have found a strong association between the Doppler findings indicating high resistance to arterial flow on both sides of placenta (BFC I-III and UAS 3-4) and placental ischemic changes expressed as the presence of infarctions and high ischemic score (Table III). The increased inflammatory response that characterises both placental ischemic changes and deciduitis can have contributed to these hemodynamic changes.

In the present study, chronic deciduitis (grades D2 and D3) was seen only in the high-risk pregnancies with the exception of one case. Our findings regarding deciduitis are very similar to those reported by others when describing chronic deciduitis in the placental basal plate [14]. Moreover, the diffuse decidual leukocytoclastic necrosis of decidua basalis, a placental lesion associated with preeclampsia, preterm birth and IUGR, also shows a significant association to chronic deciduitis [15]. In addition, chronic deciduitis has been shown to have a weak but significant association to periventricular leukomalacia in the infants [16].

An increased maternal systemic inflammatory response has been shown in preeclamptic

pregnancies where placenta inflammation plays a central role [17]. Based on our

findings, we hypothesise that the hemodynamic changes shown by Doppler velocimetry

might be a result of an abnormally increased placenta inflammation secondary to the

inflammatory process that accompanies placental ischemia, in particular the infarctions

with extensive polymorphonuclear infiltration around necrotic areas and with increase

in inflammation of decidua basalis. Such augmented inflammatory activity will result in

an amplified production of inflammatory cytokines and tumor necrosis factor (TNF)

that can directly affect the uterine circulation. In addition, the inflammatory process can

also activate leukocytes, especially granulocytes that can stimulate endothelial cells of

the uterine vessels and promote anchoring of inflammatory leukocytes with resulting

endothelial cell damage [18]. Such process would be then an integral part of the

excessive inflammatory response. There is evidence that leukocytes in uterine

circulation are significantly activated and uterine venous blood shows higher

concentration of TNFα in preeclampsia [19,20].

Thus, independent of its possible etiology, chronic deciduitis indicates an increased

inflammatory response that strengthens the role of inflammation in placental pathology.

Recent work showed that the maternal levels of inflammatory cytokines are related to

the degree of inflammatory infiltration in placental tissue samples [21]. The cytokine

and chemokine levels in the group with signs of inflammation were generally higher

than in controls but lower than in cases with histological chorioamnionitis group [21].

The above described inflammatory processes in the placenta leading to systemic

inflammatory response in maternal circulation might contribute to the chronically

increasing placental resistance to flow in IUGR and preeclampsia. This seems to be indirectly supported by the experimental work on pregnant sheep with intact placenta where embolization of a very large proportion of placenta was necessary to increase the umbilical artery resistance detectable by Doppler ultrasound [22].

In summary, our study showed placental ischemic morphological changes to be associated with Doppler ultrasound signs of increased resistance to arterial blood flow both on the fetal and maternal sides of the placenta. No significant relation to the uterine or umbilical venous flow velocities was found.

Acknowledgements

Declaration of interest

The authors report no declaration of interest.

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Legends

Fig. 1   Grades of chronic deciduitis. Histological sections from decidua basalis

showing grade D0 without inflammatory cells (fig. 1A), grade D1 with

occasional inflammatory cells (fig. 1B), grade D2 characterized by several foci

of inflammatory cells (fig. 1C), and grade D3 with diffuse infiltration by

inflammatory cells (fig. 1D). Samples stained with hematoxylin-eosin;
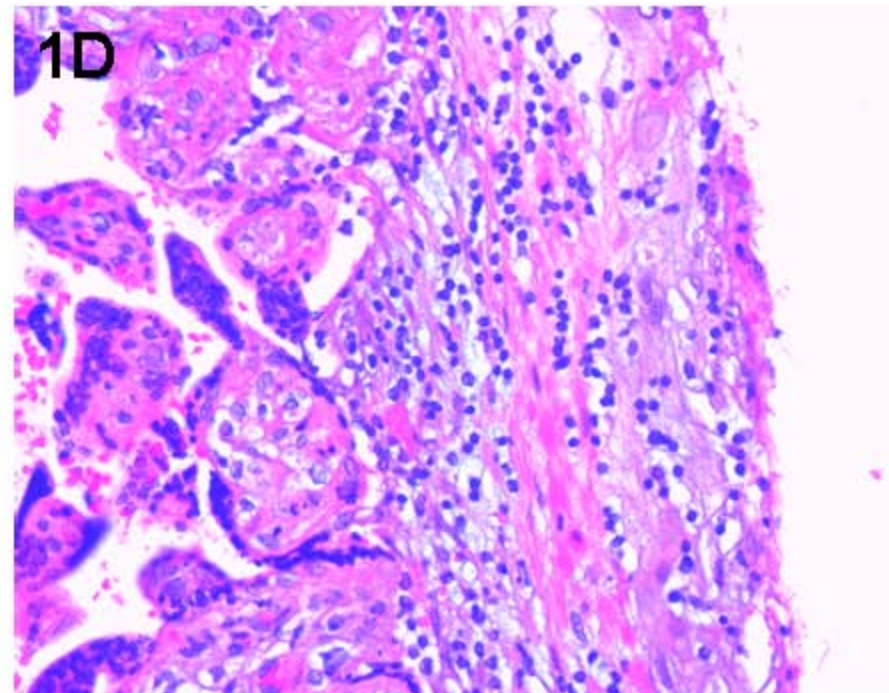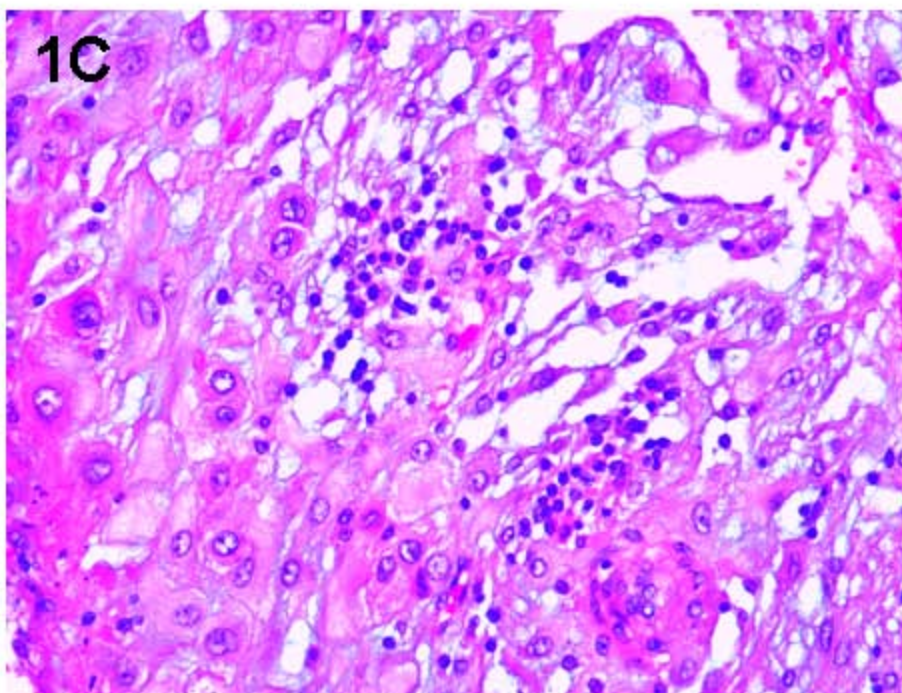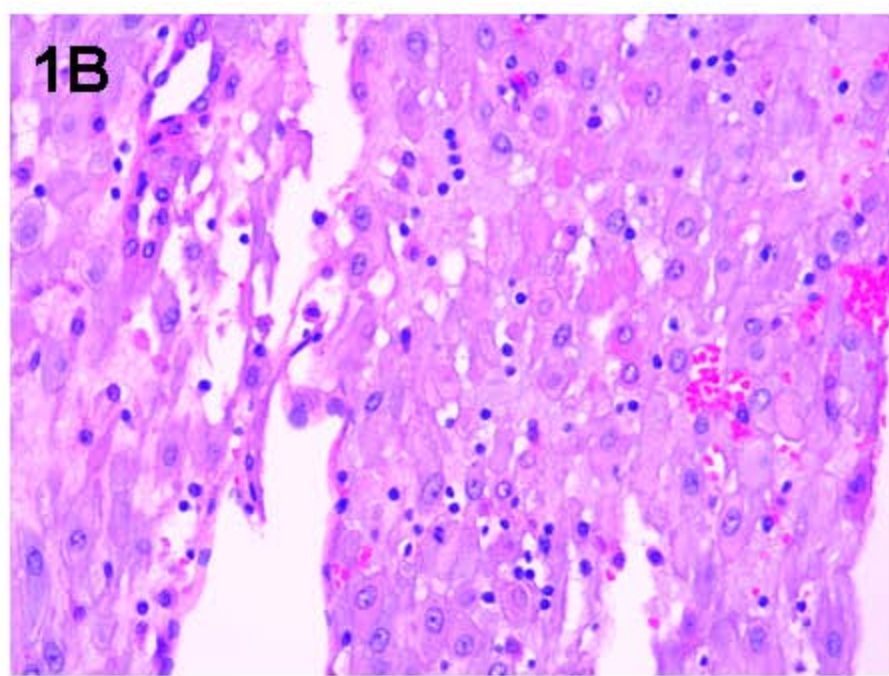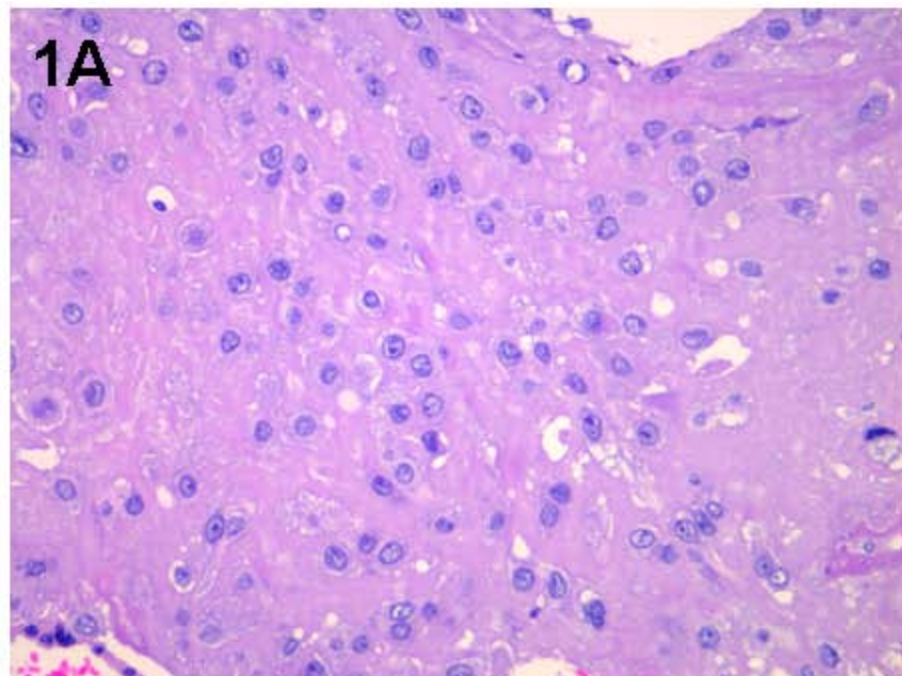
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Table I. Demographic data

	Uncomplicated pregnancies	High-risk pregnancies
n	14	31

Mothers / pregnancies

	Uncomplicated pregnancies	High-risk pregnancies
Age (years; median (range))	32 (24-42)	29 (20-42)
Nulliparae (n [%])	5 [36%]	20 [66%]
Body Mass Index* (kg/m^2; mean ± SD)	27.7 ± 4.3	28.1 ± 5.1
≤ 30 kg/m^2 (n)	10	18
31-34 kg/m^2 (n)	2	3
> 35 kg/m^2 (n)	1	1
Gestational age (weeks + days; median (range))		
- at examination	32+3 (24+2 – 39+3)	29+0 (23+0 – 37+3)
- at delivery	39+6 (38+0 – 41+0)	29+1 (23+4 – 39+4)
Delivery mode (n [%])		
- vaginal spontaneous	13 [93 %]	8 [26 %]
- cesarean section	1 [7 %]	23 [74 %]
- elective	1	6
- emergency	0	17

Newborns

Female gender (n [%])	7 [50 %]	17 [55 %]
Birth weight (g; median (range))	3590 (2670 – 4220)	1113 (320 – 3425)
Birth weight deviation ** (%; (range))	1.5 (-19 - +25)	-29.3 (-59 - +9)
Small-for-gestational age (n [%])	0	21[68 %]
Large-for-gestational age (n [%])	1 [7 %]	0
Apgar score 5 min < 7 (n [%])	0	1 [2 %]***
pH umbilical artery (mean ± SD)	$7.26 \pm 0.09^{\S}$	$7.28 \pm 0.06^{\S\S}$

* missing in 10 cases; ** deviation from the expected birth weight according to the Swedish growth standard[23]; *** 3 cases of intrauterine death excluded; § missing in 1case, §§ missing in 6 cases

Table II. Placenta morphology.

	Uncomplicated pregnancies	High-risk pregnancies	Significance of difference
n	14	31	
Placenta weight (g; median (range)) at delivery	560 (480 – 770)	330 (90 – 630)	p < 0.001
Placenta weight (g; median (range)) at morphological examination	417(325 – 527)	208 (77- 486)	p < 0.001
Ischemic score (IS) (n)			
0-1	13	9	p < 0.001*
2-6	1	16	
7-9	0	6	
(median (range))	0 (0-2)	4.5 (0-9)	
Ischemic score index (ISI)			
(median (range))	0 (0-0.4)	0.86 (0-1.75)	p < 0.001
Deciduitis (n)			
0	9	19	p = 0.07**
1	4	1	
2	1	6	
3	0	5	
Infarctions (n)			
0 %	14	16	p < 0.01***
1% - 9%	0	7	
10% - 40%	0	8	

*   IS 0-1 vs IS 2-9
**   Deciduitis 0-1 vs 2-3
*** Infarctions 0% vs 1-40%

Table III. Doppler velocimetry of umbilical and uterine circulation according to placental morphology.

	Umbilical artery blood flow class		Uterine artery score		Uterine venous flow type	
	normal	I - III	0 -2	3 - 4	I	II - III
Ischemic score 0-1	19	3	20	1	19	3
2-9	8	15	5	19	15	8
Significance of difference	p < 0.001		p < 0.001		p = 0.17	
Ischemic score index median (range)	0 (0-1.5)	0.88 (0-1.75)	0 (0-1.20)	0.88 (0-1.75)	0 (0-1.75)	0.41 (0-1.5)
Significance of difference	p < 0.001		p <0.001		p = 0.21	
Deciduitis 0-1	19	14	20	13	25	8
2-3	8	4	6	6	9	3
Significance of difference	p = 0.74		p = 0.73		p = 1.00	
Infarctions no	22	8	25	5	25	5
yes	5	10	1	14	9	6
Significance of difference	p = 0.02		p < 0.001		p = 0.14	

Results presented as numbers or median (range).