Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Evaluation of placental vascularization by three-dimensional ultrasound examination in second and third trimester of pregnancies complicated by chronic hypertension, gestational hypertension or pre-eclampsia

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ARTICLE INFO

Article history:
Received 14 October 2016
Received in revised form 27 January 2017
Accepted 17 March 2017
Available online xxxx

Keywords:
3-Dimensional ultrasound
Chronic hypertension
Gestational hypertension
Placenta
Pre-eclampsia
Vascularization

ABSTRACT

Objectives: The purpose of this study was to assess three-dimensional placental power Doppler indices in second and third trimester of pregnancies complicated by chronic-, gestational hypertension or pre-eclampsia.

Methods: We analyzed 226 pregnancies prospectively measuring three-dimensional placental power Doppler indices (vascularization index, flow index, vascularization flow index) in cases of normal blood pressure (N = 109), chronic hypertension (N = 43), gestational hypertension (N = 57) and pre-eclampsia (N = 17). We evaluated the correlation among vascularization indices, flow characteristics of uterine arteries and perinatal outcome. We assessed the influence of maternal factors (pregestational body mass index, previous pregnancies/deliveries, maternal age) on vascularization indices, and analyzed histological findings of placenta from pregnancy hypertension groups.

Results: Vascularization index was significantly higher ($p = 0.010$) in pregnancies with chronic- and lower ($p = 0.152$) in pregnancies with gestational hypertension and preeclampsia compared to the normal group. Flow index was significantly lower in all three pathological groups compared to normal group. Placental volume was significantly smaller ($p < 0.001$) in all three pathological groups than in normal pregnancies at the time of delivery, and there was no significant difference between the three affected groups. The rate of adverse pregnancy outcomes showed no significant difference between the normal and chronic hypertension groups. We observed significantly lower 1′, 5′ and 10′ APGAR scores ($p < 0.,001$), and birth weight in preeclampsia compared to chronic-, gestational hypertension, and normal groups. Maternal factors had no influence on the development of the power Doppler indices.

Conclusion: Vascularization indices seem good markers for the prediction of risks and adverse outcomes in case of pregnancy hypertension.

1. Introduction

Hypertension during pregnancy affects 5–7% of all pregnancies and approximately 70% of cases occur in first-time pregnancies [1]. The incidence of chronic hypertension (CHT) among pregnant women is 1–2%, while gestational hypertension (GHT) complicates 3–6% of all cases showing a rising tendency in recent years [1,2]. It is a prominent cause of maternal and fetal morbidity and mortality; however, its pathophysiological background is poorly understood [3]. Most patients have no clinical symptoms, but it is important to emphasize that hypertension is merely one manifestation, i.e., the first stage of pre-eclampsia (PE).

Proper uterine and placental vascularization is important for the adequate development of pregnancies [4]. Pathological fetomaternal circulation can lead to elevated resistance in uterine circulation, which can cause placental insufficiency [5,6] and thus – due to pathological development of the placenta – result in premature birth, intrauterine hypoxia, or even intrauterine death [7,8].

Abbreviations: 3D, three-dimensional; 3-DPD, three-dimensional power Doppler; BMI, body mass index; CHT, Chronic Hypertension; FI, Flow Index; GHT, Gestational Hypertension; IUGR, Intrauterine Growth Restriction; NBP, Normal Blood Pressure; PE, Pre-eclampsia; PI, Pulsatility Index; VFI, Vascularization Flow Index; VI, Vascularization Index; VOCAL, Virtual Organ Computer-aided AnaLysis.

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http://dx.doi.org/10.1016/j.preghy.2017.03.004
2210-7789/

Improvements in three-dimensional (3D) ultrasound have allowed us to obtain and study volumes from different organs, such as the human placenta more precisely [9], and the color map provided by power Doppler has made the study of vessels with low resistance much easier [10]. The combination of these techniques has made it possible to study the morphology of the vascular tree and to quantify the total blood flow of the placenta [11].

The purpose of the present investigation was to reveal changes in vascularization and their effects on perinatal outcome using Doppler indices of uterine arteries and placental vascularization during the second and third trimester.

Our hypothesis was that despite ongoing antihypertensive treatment placental vascularization and placental volume do differ, depending on the etiology of hypertension (CHT or GHT). We aimed to explore the causes affecting placental volume and vascularization, and analyzed the influence of gestational (placental volume, gestational age, flow characteristics of umbilical and uterine arteries, perinatal outcome and complications) as well as maternal characteristics (maternal age, pregestational body mass index (BMI), previous pregnancies and deliveries) on placental vascularization.

2. Materials and methods

Women with singleton pregnancies who presented for routine ultrasound between September 2014 and November 2015 once in the second or third trimester at the Department of Obstetrics and Gynecology, University of Szeged were enrolled in our prospective cohort study, which was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for research involving humans. We received informed consent from each participant, and our study was approved by the institutional research ethics committee (No.: 32/2014).

Pregnancies enrolled during the examination period were divided into four groups: normal blood pressure as control group (NBP) (N_{NBP} = 109), patient group consisting of pregnancies complicated by chronic hypertension (N_{CHT} = 43), pregnancies complicated by gestational hypertension (N_{GHT} = 57) and pregnancies complicated by pre-eclampsia (N_{PE} = 17). It was not our goal to include similar number of patients in each study group, but to include as many gestational hypertension cases detected during the study-period as possible.

Exclusion criteria included multiple pregnancies; thrombophilia, molar pregnancy, structural or chromosomal anomaly and fetal abnormalities (with 1 month follow-up after delivery); placenta praevia; self-reported drug, alcohol, caffeine or nicotine abuse; exposure to circulatory medications (calcium dobesilate); systemic diseases (such as diabetes mellitus, vasculitis, etc.).

We specified high blood pressure on the basis of the International Society for the Study of Hypertension in Pregnancy [12] (≥140 mmHg systolic and/or ≥90 mmHg diastolic). During blood pressure measurement patients were seated comfortably, their arm was relaxed, uncovered, supported at the level of the heart, and their arm circumference was also measured to use the proper cuff size. Blood pressure was measured three times (BP A100 PLUS, Microlife AG, Windau, St. Gallen, Switzerland) on each occasion, and patients were scheduled for a check-up every two weeks. The patients were prepared for self-control blood pressure measurement as well.

All patients of the three pathological groups had ongoing antihypertensive therapy via oral administration of 250 mg alpha-methyldopa (Dopegyt, EGIS Pharmaceuticals PLC., Budapest, Hungary) and dietary salt restriction at the time of inclusion.

High blood pressure prior to pregnancy was determined as inclusion criteria for CHT [12]. New onset of hypertension after 20 weeks of gestation was an inclusion criterion for GHT, and NBP was documented both before pregnancy and during the entire pregnancy period [12]. Patients in the pre-eclampsia group (PE) had high blood pressure during gestation associated with proteinuria or intrauterine growth restriction [12].

Body mass index (BMI) was defined as underweight if <19 kg/m^2 and as obese if >29 kg/m^2.

2.1. Management of the examinations

All patients were scanned in a semi recumbent position by the same sonographer with the help of Voluson 730 system (RAB 2-5 MHz transducer; GE Healthcare Austria, Tiefenbach, Austria). Same instrumental settings were used in all cases ('Obstetrics/2–3 trimester' in 2D mode). An initial two-dimensional conventional examination provided data about fetal position, body movements and fetal heart rate, placental localization, insertion of umbilical cord, the volume of amniotic fluid and fetal biometry according to the formula B of Hadlock [13], followed by two-dimensional color Doppler investigation of uterine arteries [14], where pulsatility index (PI) was measured as well [15].

2.2. Volume acquisition

We used 3D rendering mode, in which the color and gray value information was processed and combined to give 3D image (mode cent: smooth, 4/5; FRQ: low; quality: 16; density: 6; enhance: 16; balance: 150; filter: 2; actual power: 2 dB; pulse repetition frequency: 0.9). Power Doppler window (pulse repetition frequency at 900 Hz and wall filter of 50 Hz) was placed over the placenta, mapping the vascular tree from basal to chorionic plates. This technique produces higher sensitivity, because it is based on amplitude instead of mean frequencies, unlike color Doppler to depict the vascular tree [10]. Moreover, color mapping is independent from the angle of insonation and does not show 'aliasing' [10,16,17]. The 3D static volume box was placed over the highest villous vascular density zone at umbilical cord insertion [8,18]. We used low resolution acquisition to avoid any kind of artifacts [18].

2.3. Calculation of three-dimensional power Doppler indices (3-DPD)

Volume files were analyzed using virtual organ computer-aided analysis (VOCAL) software (4D View® Version 10.4, GE Healthcare Austria, Tiefenbach, Austria) by an expert in 3D analysis.

We used Mercé-type placental sonobiopsy (see Fig. 1), a reproducible, validated method for obtaining representative sample of the placental tree, which – contrary to other methods – is applicable throughout the whole pregnancy when the entire placenta needs to be visualized [18,19]. This method is a valid alternative for the evaluation of the placental vascular tree when visualization of the entire placenta is not possible [20]. The spherical sample volume was constantly 28 ml. Color scale values were calculated automatically in a histogram by VOCAL software from the acquired spherical sample volume in all cases [8,18]. Two-dimensional and three-dimensional acquisitions were performed at the same time, and 3D volume files were analyzed by VOCAL software at a later time.

2.4. Statistical analysis

Statistical analyses were performed by IBM SPSS Statistics 21.0 for Windows (IBM, New York, USA). Kolmogorov–Smirnov test results were significant for our database demonstrating that our study samples were not normally distributed. Kruskal–Wallis tests

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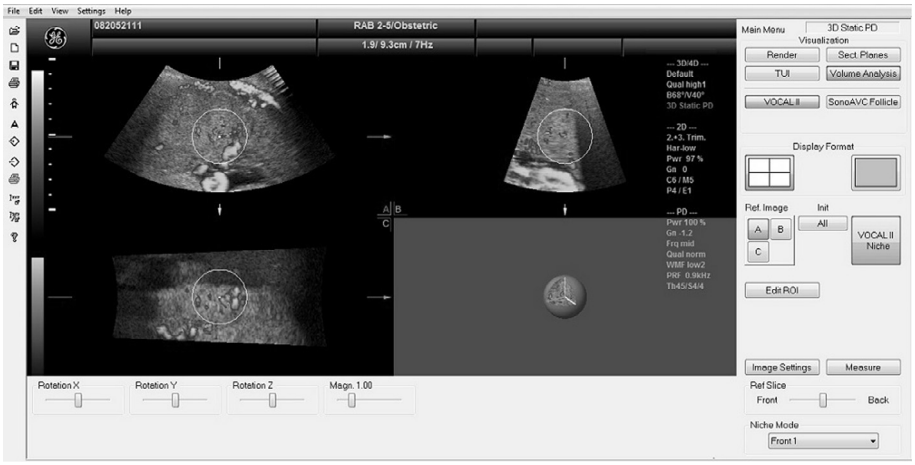

Fig. 1. Interface of VOCAL software presenting placental sonobiopsy at umbilical cord insertion (32nd week of gestation).

were used for comparison of continuous variables depending on the four groups (CHT versus NBP; GHT versus NBP; PE versus NBP), whereas comparison between the three pathological groups (CHT versus GHT; GHT versus PE) was assessed with Mann–Whitney *U* test. Univariate comparisons for categorical variables were assessed by χ^2 tests. Linear regression coefficient values and equations depending on gestational age were also calculated for VI, FI, and VFI in case of pathological and control groups. Association between placental 3-DPD indices, maternal and fetal characteristics, two-dimensional color Doppler indices (PIs of umbilical and uterine arteries) were determined by Spearman's rank correlations and the multivariate relationship was analyzed using quantile regression.

2.5. Histological analysis

Histological analysis of placentae following delivery were performed in 18 cases of pregnancy hypertension/5 CHT, 8 GHT and 5 PE/. Histological preparations were made on the basis of the recommendation of The Royal College of Pathologists, UK. [21] We applied AxioVision SE64 Rel. 4.9.1 program for assessing slides.

3. Results

The analysis of 3D volume acquisition demonstrated that VI indices are significantly higher in CHT group ($p = 0.010$) compared to NBP. In case of GHT, VI was lower compared to NBP ($p = 0.152$) group, though the difference was not statistically significant. There was significant difference ($p < 0.001$) between CHT and GHT groups.

All PE cases evolved from GHT cases, therefore we analyzed the changes in 3-DPD indices, but the difference between GHT and PE groups in case of VI was not statistically significant ($p = 0.175$).

FI was significantly lower in all pathological groups compared to NBP group (in case of CHT $p = 0.009$, in case of GHT and PE $p < 0.001$). There was no statistically significant difference between CHT and GHT ($p = 0.296$) and GHT and PE ($p = 0.183$) groups.

Significantly different VFI was found between CHT and GHT groups and when PE group was compared to NBP group, respectively (see details in Table 1).

Spearman rank order correlation test was utilized for seeking correlation between 3-DPD indices and birth weight. Strong linear correlation was found between VI, FI and birth weight ($p = 0.002$).

Table 1
Mean value and standard deviation (SD) of 3-dimensional power Doppler (3-DPD) indices (VI: vascularization index, FI: flow index, VFI: vascularization flow index) and the rate of early diastolic notch in normal blood pressure (NBP), chronic hypertension (CHT), gestational hypertension (GHT) and pre-eclampsia (PE) with level of significance.

	CHT (N=43)	NBP (N=109)	GHT (N=57)	PE (N=17)
VI (mean ± SD)	14.42 ± 10.12	10.36 ± 6.19	7.73 ± 7.07	4.86 ± 3.22
	p=0.010	p=0.152	p=0.175	
	p=0.001			
FI (mean ± SD)	41.51 ± 8.15	46.08 ± 7.75	38.50 ± 9.60	36.5 ± 5.71
	p=0.009	p=0.000	p=0.183	
	p=0.141			
VFI (mean ± SD)	3.61 ± 2.81	4.08 ± 2.51	3.02 ± 2.45	1.99 ± 1.6
	p=0.973	p=0.075	p=0.128	
	p=0.002			
Early diastolic notch	1/44 (2.27%)	0/146 (0%)	3/38 (7.89%)	6/17 (36.29%)
	p=0.126	p=0.004	p=0.012	

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Furthermore we could establish that in case of VFI values equal to or lower than 2.6 intrauterine growth restriction (IUGR) – and according to ISSHP's revised statement [12] progression to PE – will develop. Mean FI was 45.7 in case of normal pregestational-BMI and 41.2 in case of elevated BMI, thus elevated pregestational-BMI had substantial influence on FI depression ($p < 0.05$) and fetal growth development, consequently on birth weight. The placental volume at the time of delivery was significantly ($p < 0.001$) smaller in GHT, CHT and PE groups than in NBP, but there was no significant difference between the pathological groups.

Early diastolic notch findings are presented in Table 2. The number of previous pregnancies and deliveries in each group is

Table 2
Maternal characteristics of pregnancies with normal blood pressure (NBP), chronic hypertension (CHT), gestational hypertension (GHT) and pre-eclampsia (PE). Significant differences are highlighted.

		CHT (N=43)	NBP (N=109)	GHT (N=57)	PE (N=17)
Mean maternal age (mean ± SD)		32.8 ± 4.2	30.7 ± 4.7	31.1 ± 5.4	29.2 ± 5.4
Weeks of gestation *at the time of 3D sweep* (mean ± SD)		$28^{+5} \pm 6^{+6}$	$24^{+6} \pm 7^{+2}$	$30^{+2} \pm 6^{+2}$	$31+^{4} \pm 5^{+9}$
Weeks of gestation *at the time of delivery* (mean ± SD)		$38^{+4} \pm 1^{+4}$	$38^{+3} \pm 1^{+6}$	$38^{+1} \pm 2^{+3}$	$37+^{2} \pm 2^{+4}$
Premature birth		3/43 (4.76%)	8/109 (7.33%)	7/57 (12.28%)	5/17 (29.41%) p<0.001
Pregestational-BMI (kg/m²)		31.8 ± 4.6	30.7 ± 5.2	31.0 ± 5.0	27.2 ± 6.1
Previous pregnancies	**None**	14/43 (34.88%)	35/109 (32.11%)	16/57 (28.07%)	6/17 (35.29%) p<0.001
	One	12/43 (27.90%)	37/109 (33.94%) p<0.001	27/57 (47.36%) p<0.001	4/17 (23.52%)
	Two or more	17/43 (39.53%)	38/109 (34.86%) p<0.001	14/57 (24.56%) p<0.001	7/17 (41.17%)
Previous deliveries	**None**	17/43 (39.53%) p<0.001	51/109 (46.78%) p<0.001	33/57 (57.89%) p<0.001	7/17 (41.17%)
	One	17/43 (39.53%)	38/109 (34.86%)	20/57 (35.08%)	6/17 (35.29%)
	Two or more	9/43 (20.93%)	20/109 (18.34%)	4/57 (7.01%) p<0.001	4/17 (23.52)

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Table 3
Perinatal characteristics and pregnancy outcome in cases of normal blood pressure (NBP), chronic hypertension (CHT), gestational hypertension (GHT), and pre-eclampsia (PE). Significant differences are highlighted.

		CHT (N=43)	NBP (N=109)	GHT (N=57)	PE (N=17)
Apgar score (mean ± SD)	**1'**	8.92±1.11	9.07±1.50	8.68±1.51	8.38±1.47
			p<0.001	p<0.001	
	5'	9.71±0.83	9.70±0.95	9.61±0.72	9.38±1.38
				p<0.001	
	10'	9.92±0.34	9.83±0.77	9.82±0,60	9.61±0.80
				p<0.001	
Umbilical pH (mean ± SD)		7.22±0.07	7.26±0.07	7.26±0.07	7.25±1.05
Perinatal complications	**Apnea**	3/43 (6.97%)	9/109 (8.25%)	6/57 (10.52%)	7/17 (41.17%)
					p<0.001
	Polycythemia	2/43 (4.64%)	7/109 (6.42%)	7/57 (12.28%)	2/17 (11.76%)
			p<0.001		
	Hypoglycemia	1/43 (2.32%)	2/109 (1.83%)	2/57 (3.50%)	3/17 (17.64%)
					p<0.001
	Respiratory distress syndrome	0/43 (0%)	0/109 (0%)	0/57 (0%)	3/17 (17.64%)
					p<0.001
	Dysmaturity	0/43 (0%)	3/109 (2.75%)	4/57 (7.01%)	12/17 (70.58%)
			p<0.001		
	Feeding difficulties	1/43 (2.32%)	7/109 (6.42%)	4/57 (7.01%)	0/17 (0%)
	Parenteral administration of ampicillin	4/43 (9.30%)	1/109 (0.91%)	4/57 (7.01%)	5/17 (29.41%)
		p<0.001	p<0.001	p<0.001	
Birth weight (g)		3377±374	3346±555	3236±751	2422±817
					p<0.001
Male/female ratio		32.5%/67.5%	47.7%/52.3%	54.3%/45.7%	35.3%/64.7%

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Table 4
Effects of maternal and fetal characteristics on placental vascularization indices in case of pregnancy hypertension (chronic-, gestational hypertension and preeclampsia cases examined as one)* – statistical methods used, and level of significance (N.S.: *no significant difference*, S.: *significant difference* was found).

Table 4	Statistical method	VI	FI	VFI	p-value
Gravidity	ANOVA	N.S.	N.S.	N.S.	<0.001
Parity	ANOVA	N.S.	N.S.	N.S.	<0.001
Pregestational BMI (normal)	ANOVA	N.S.	N.S.	N.S.	<0.04
Pregestational BMI (obese)	ANOVA	N.S.	N.S.	N.S.	<0.04
Pregestational BMI (excessive weight gain)**	ANOVA	N.S.	N.S.	N.S.	<0.04
Umbilical cord arterial pH	Student's *t* test	N.S.	S	N.S.	<0.001
1-minAPGAR score	Mann-Whitney test	N.S.	N.S.	N.S.	<0.47
5-minAPGAR score	Mann-Whitney test	S.	S.	S.	<0.04
10-minAPGAR score	Mann-Whitney test	S.	S.	S.	<0.046
Birth Weight	Student's *t* test	S.	S.	S.	<0.01
Estimated Fetal Weight	Student's *t* test	S.	S.	S.	<0.01
Placental localisation	Student's *t* test	N.S	N.S.	N.S.	<0.04

* There was no significant difference between the pathological groups.
** Normal BMI pregestationally with excessive weight gain during pregnancy.

recorded in Table 3. Risk estimation for perinatal complications (such as apnea, respiratory distress syndrome (RDS), hypoglycemia, polycythemia, dysmaturity, feeding difficulties etc.) was also analyzed by using Wilcoxon rank-sum test. FI value was found prognostic for umbilical pH and birth weight, but there was no difference between CHT, GHT or PE groups (see details in Table 3).

We found that BMI and other maternal characteristics had no effect on placental vascularization indices in pregnancies either complicated by hypertensive disorder or not (see Table 4).

There was correlation ($p < 0.05$) between NOTCH detected and pregnancy outcome as in case of NOTCH the chance of caesarean section was 65% in CHT, 77% in GHT, and 100% in PE, although we found no correlation between uterine artery PI and adverse pregnancy outcome rates.

We applied non-parametric analysis to compare three or four groups, and Mann-Whitney *U* test was used to compare the pathological groups.

Table 5
Histological characteristics of 18 placentas, in case of pregnancy hypertension/5 Chronic Hypertension, 8 Gestational Hypertension, 5 Preeclampsia/, that have been analyzed following delivery.

Histological characteristics of placentae with pregnancy hypertension	CHTN = 5	GHTN = 8	PEN = 5
Neutrophil invasion:	0/5	0/5	0/5
Interstitial fibrosis:			
-No	5/5	4/8	0/5
-Mild	0/5	4/8	3/5
-Moderate	0/5	0/8	2/5
-Severe	0/5	0/8	0/5
Vascularization:			
-Normovascularized	3/5	0/8	0/5
-Hypovascularized	2/5	8/8	5/5
Parenchymal haematoma:	2/5	6/8	3/5
Fibrin deposits:	2/5	4/8	5/5
Syncytial knots:			
-Yes	2/5	3/8	0/5
-Moderate	3/5	2/8	3/5
-Severe	0/5	3/8	2/5
Calcification:			
-None	3/5	0/8	0/5
-Peripheral	1/5	4/8	0/5
-Focal	1/5	4/8	5/5
Chorioamnionitis:	0/5	1/8	0/5
Funisitis: /same patient that had chorioamnionitis/	0/5	1/8	0/5
Villiitis:	0/5	0/8	0/5
Accelerated maturation:	1/5	6/8	5/5

Table 5 shows the main histological characteristics of each pathological group. Vasculopathy was only seen in 2/5 PE placentae, all PE cases were IUGR and two of them have been delivered preterm. Fig. 2 shows a normal blood pressure placenta, and Fig. 3 shows a placenta from a preeclamptic patient.

4. Discussion

Placental vascularization was investigated in our 2nd–3rd trimester *in vivo* study while most publications describe only 1st trimester data, and was found to be significantly lower in gestational hypertension compared to normal blood pressure.

A common pathological feature of GHT is the failure of maternal arteries supplying placenta to undergo histological adaptations of normal pregnancy that facilitate adequate placental perfusion [22,23].

In CHT cases involving predisposed pregnant women and normal placenta, maternal scavenging system takes part in pathological regulation of maternal blood pressure. This may lead to inadequate response of these systems, resulting in an overload and defect even if the vascular system of the placenta is normal. Since placenta has normal growth patterns in CHT, the development and malfunctions of maternal systems evolve more slowly than in GHT or PE. In our CHT cases placental growth was close to normal, which led to the development of milder clinical symptoms and perinatal complications than in GHT and especially in PE cases. Premature birth rate was almost 2.57 higher in GHT and 6.17 times higher in PE compared to CHT. GHT cases with IUGR were involved and no proteinuria could be detected because of antihypertensive therapy. It means that antihypertensive therapy protects maternal renal function, but placental vascularization can be destroyed [12].

In GHT cases comprising women with normal medical condition before pregnancy and dysfunctional placenta, the scavenging system of these pregnant women can cope with these deleterious changes in the placenta in the early period of gestation, then GHT and incidentally PE may develop. Clinical symptoms may only develop subsequently during pregnancy. Concurrently, maternal endothelium is affected only late in pregnancy and thus changes in placental vascularization are mostly related to PE (GHT complicated by IUGR [12]) rather than to CHT [24,25]. In this case, the fetus mostly develops into an abnormally grown baby. IUGR rate was 22.97% among GHT cases (17/74), which shows the progress rate to PE, although proteinuria and other dysfunction of maternal organs, such as renal insufficiency, liver dysfunction and neurological or hematological complications did not appear [12].

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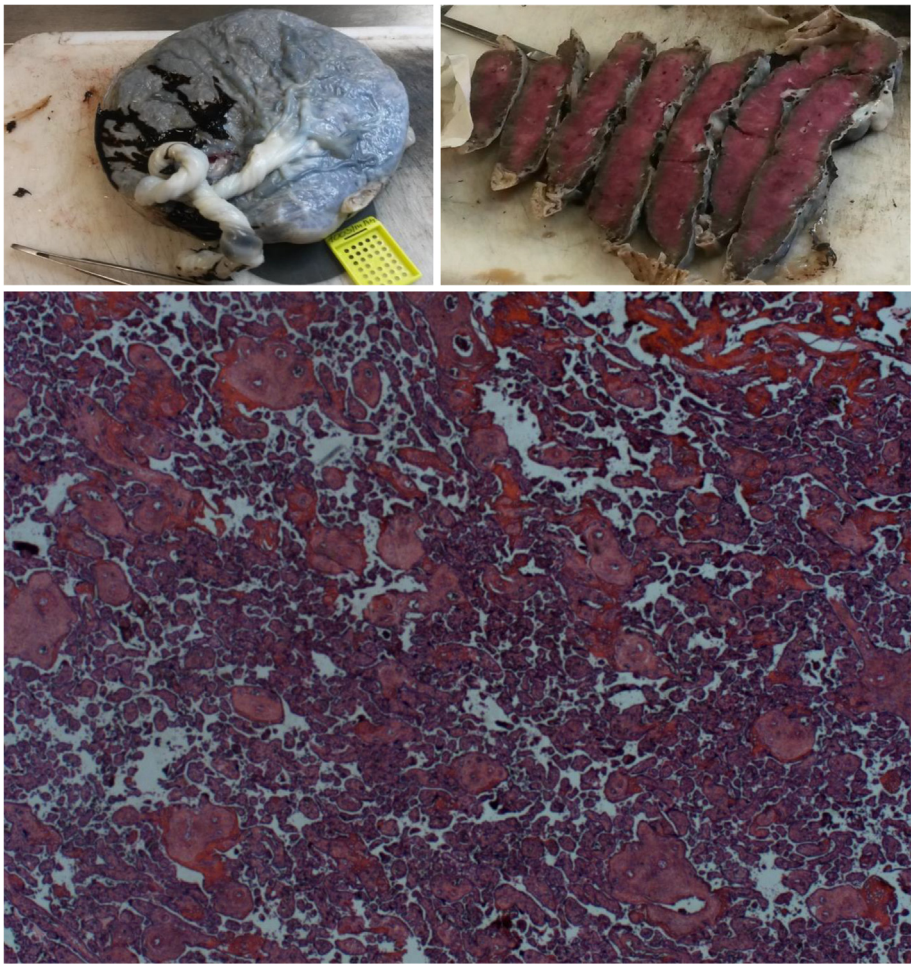

Fig. 2. Histological sample of normal placenta. Haemtoxylin-eosin staining, magnification 40×.

The placenta plays a key role in PE by releasing damaging factors into maternal circulation leading to maternal symptoms, as failed conversion of spiral arteries limits normal maternal blood flow [26] and it seems that neither the fetus, nor the uterine muscle has a role in the development of the disorder, which resolves following delivery.

We found that in second and third trimesters placental vascularization is even more significantly lower in hypertension compared to NBP cases despite ongoing antihypertensive treatment, than in first trimester [27].

Regarding CHT, significantly higher VI revealed elevated vascularization rate, because this is the placental vascular response to elevated maternal blood pressure. Significantly lower FI rate, suggests partial insufficiency of this process. There was no significant difference in adverse pregnancy outcome rates between CHT and NBP, which enhances the possibility of an underlying compensatory mechanism. This compensatory mechanism may be responsible for increased VI in pregnancies complicated by CHT. It seems that chronic hypertension leads to lower FI and higher VI during early stages of pregnancy thus the placenta may have the ability to compensate, though sometimes this compensatory mechanism is inadequate. We can highlight that CHT cases have similar placental blood perfusion to NBP cases, which is supported by the higher VI and lower FI rates and the similar adverse pregnancy outcome rates.

Our results showed lower VI in pregnancies complicated by GHT and PE compared to NBP group, though the difference was not significant. Similarly to Guiot et al. [28] and Odeh et al. [29], FI was statistically significantly lower in GHT and in PE groups compared to NBP group. We can highlight that GHT and PE cases have less placental blood perfusion than CHT or NBP, which is supported by lower VI and FI rates.

We found that placental vascularization indices in case of NBP were biostatistically constant during pregnancy. In pregnancies complicated by hypertensive disorders placental vascularization indices were decreased during pregnancy, but the registered decrease was not significant.

The fetal characteristic features of hypoxia were not elevated in CHT and GHT patients compared to NBP patients. Occurrence of apnea was about 4 times higher, while hypoglycemia was about 5 times higher in PE compared to all other groups. Since hypertension during pregnancy is determined by different maternal factors, we emphasize the influence of pregestational-BMI and primigravidity/primiparity. In case of elevated pregestational-BMI, FI decreased significantly in all three pathological groups. Primiparity has a definite role in the development of GHT. Primiparity ratio was 57.8% in GHT and 37.2% in CHT. Furthermore, in second or third pregnancies the chance of CHT rises. In our study, GHT was 35% for the second gestation, 7.2% for the third or higher number gestations. In the CHT group, the prevalence of two earlier pregnancies was 39.5% and the prevalence of three or more was 23.3%.

The male/female ratio was different between CHT and GHT in our study. Severe placental dysfunction is more common in pregnancies with a male infant than with female one [30]. This is also

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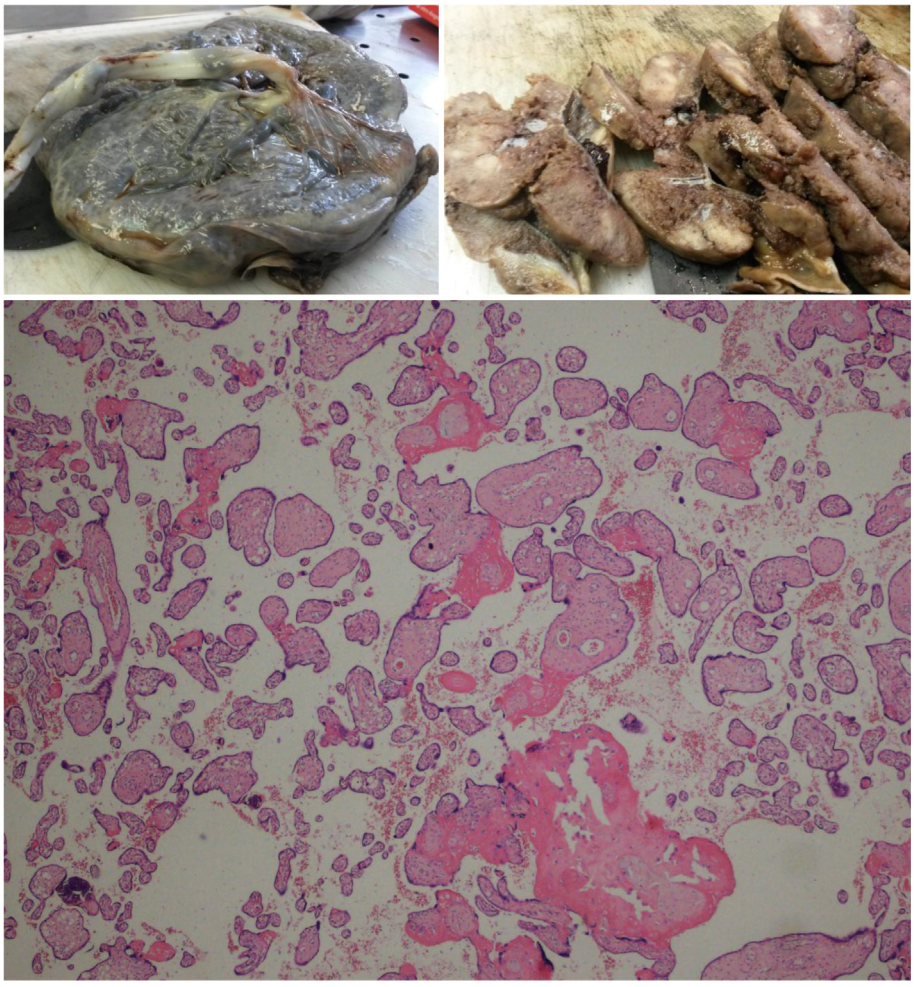

Fig. 3. Histological sample of preeclamptic placenta with intra uterine growth restriction. Small terminal villi, with villous hypoplasia, Haemtoxylin-eosin staining, magnification 40×.

confirmed by our data, because male/female ratio was 54.3% versus 45.7% in GHT, while it was 32.3% versus 67.5% in CHT presenting female dominance compared to the normal distribution of the control group (47.7% versus 52.3%).

In spite of the fact that alpha-methyldopa therapy and dietary salt restriction were already ongoing at the time of inclusion, we found significant differences in placental vascularization between the three pathological groups in second and third trimester, which shows the partial effectiveness of antihypertensive therapy and the potential risk of progression to PE. Although Noguchi et al. [31] found that 3-DPD placental vascularization indices at 18–22 weeks could not be used to predict high-risk pregnancies that develop GHT in a low-risk population, our results showed their usefulness probably because of the difference in the weeks of gestation and the number of cases examined.

We have still insufficient amount of data on possible correlations of Doppler analyses to clinical biomarkers of CHT, GHT and/or PE, such as soluble fms-like tyrosine kinase 1 (sFlt-1) or placental growth factor (PlGF) [32].

5. Conclusions

Our goal was to examine placental vascularization in 2nd and 3rd trimester, on etiological basis. We found that in early detection of PE, 3-DPD indices may be useful to prevent the most frequent fetal complications, thus we can make the decision about management and monitoring strategy.

Funding

Financial support was provided by the Foundation for Reproductive Health in the Southern Great Plain-2000.

Conflicts of interest notification

The authors report no conflicts of interest.

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