CORRELATION BETWEEN PREGNANCY HYPERTENSION TYPES FROM THE POINT OF VIEW OF PLACENTAL VASCULARIZATION INDICES MEASURED BY 3-DIMENSIONAL POWER DOPPLER

Ph.D. Thesis

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List of publications

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2. Abbreviations

2-D	two-dimensional
3-D	three-dimensional
AC	abdominal circumference
ACOG	American College of Obstetrics and Gynecology
AUtPSV	uterine artery peak systolic velocity
BMI	body mass index (kg/m2)
BPD	biparietal diameter
CHT	chronic hypertension
CRL	crown rump length
EFW	estimated fetal weight
FI	flow index
FL	femur length
GA	gestational age
GDM	gestational diabetes mellitus
GHT	gestational hypertension
HC	head circumference
ISSHP	International Society for the Study of Hypertension during Pregnancy
IUGR	intrauterine growth restriction
NBP	normal blood pressure
OGTT	oral glucose tolerance test
PD	power Doppler
PE	pre-eclampsia
PI	pulsatility index
RDS	respiratory distress syndrome
RI	resistance index
VOCAL	virtual organ computer-aided analysis
VFI	vascularisation flow index
VI	vascularisation index (%)
WHO	World Health Organization

3. Introduction

The placenta has many important functions: separates and connects. On one hand separates the fetal and maternal circulation from each other through epithelial cells of placental villi. On the other hand, supplies the fetus with sufficient nutrients and oxygen, providing optimal conditions for the development of the fetus. Therefore, the adequate placental vascularisation is essential a for the intrauterine physiologic development. It is well known, that maternal high blood pressure, either chronic or gestational, reduces he efficacy of utero-placental circulation, increases vascular resistance, because during placental development in spiral arterioles the increase in vessel diameter, performed by cytotrophoblasts that replace the endothelium and the muscular layer of arterioles, is smaller. On the other hand, the perfusion of the pregnant uterus is increased by significant increase in maternal factors such as blood volume, cardiac output, and pulse and significant decrease in blood viscosity. The above mentioned anatomical and physiological changes, hand in hand, worsen fetal oxygenation and nutrition, that can be easily detected by ultrasonographical measurements of placental vascularization.

Conventional two-dimensional (2D) ultrasound can provide many important information on normal or pathological placental morphology, but it is not suitable for three-dimensional (3D) examination of placental vascularization. In-vivo functional examination of the placenta by 3D can provide crucial additional information on placental vascularization and intensity of blood flow. With the help of power Doppler technique (3-DPD) and Virtual Organ Computer-aided Analysis (GE Medical Systems, Austria, version 10.4) we get objective and reproducible data on placental vascularization.

In case of pregnancy hypertension placental vascularization is worse than in normal blood pressure placentas. As a result of that, newborns will have lower birth weight, and may will develop intrauterine growth restriction (IUGR), furthermore more complications can occur in neonates. Unfortunately, there is no specific screening method for clinicians to distinguish between high risk patients that will develop adverse pregnancy outcome from those that doesn't. It is known that 25% of pregnancies with chronic- and gestational hypertension will develop pre-eclampsia (PE), that is a severe clinical manifestation of pregnancy hypertension, and there is no specific screening method with high specificity and sensitivity to predict it in early pregnancy. The analyses of placental vascularization with 3-DPD and VOCAL may be useful in early prediction of utero-placental abnormalities, then methods based on conventional ultrasonographical screening methods.

The prevalence of pregnancy hypertension was around 3-6% in Hungary during recent years, mainly because of increasing mean maternal age. That is the reason why early screening of pregnancies at risk is important, to prevent possible complications.

4. Hypothesis

1. At the beginning of the present study we hypothesized that there is negative correlation between 3-DPD vascularisation indices and the severity of pregnancy hypertension type with which the pregnancy is complicated.
2. We also hypothesized that there is correlation between AUtPSV values and the presence of gestational diabetes, as a complication, in case of pregnancy hypertension.

5. Aims of the investigation

1. To evaluate and compare 3-DPD placental vascularization indices in case of case group of pregnancy hypertension and control group of normal blood pressure pregnancies.
2. To evaluate and compare 3-DPD placental vascularization indices between pathological groups of chronic-, gestational hypertension and preeclampsia.
3. To test the hypothesis that there is negative correlation between 3-DPD placental vascularization indices and the severity of pregnancy hypertension type.
4. To compare 3-DPD placental vascularization indices and maternal characteristics between pregnancy hypertension types (CHT, GHT and PE).
5. To compare 3-DPD placental vascularization indices and fetal characteristics between pregnancy hypertension types (CHT, GHT and PE).
6. To compare 3-DPD placental vascularization indices and neonatal characteristics between pregnancy hypertension types (CHT, GHT and PE).
7. To compare 3-DPD placental vascularization indices and adverse pregnancy outcome rates between pregnancy hypertension types (CHT, GHT and PE).
8. To test the hypothesis that there is correlation between AUtPSV values and the presence of gestational diabetes, as a complication, in case of pregnancy hypertension.
9. To evaluate 3-DPD vascularization indices and AUtPSV in case of pregnancy hypertension complicated with gestational diabetes mellitus (CHT+GDM, GHT+GDM).

10. To compare prenatal ultrasonographical findings (vascularization-, flow- and vascularization-flow index) of the placentas, from pregnancy hypertension case groups, to the severity of histological findings following delivery.

6. Materials and Methods

Women with singleton pregnancies were included seen once in second or third trimester at our outpatient clinic at Department of Obstetrics and Gynecology, University of Szeged. The study was carried out between 2014 and 2015. our study was approved by the institutional research ethics committee: 2014/32.

6.1. Diagnostic criteria for hypertension

High blood pressure (>140 mm Hg systolic or >90 mm Hg diastolic) was defined on the basis of the International Society for the Study of Hypertension in Pregnancy (ISSHP) (3). Blood pressure was measured (BP A100 PLUS, Microlife AG, Windau, St. Gallen, Switzerland) three times on each occasion.

Patients in the case groups (CHT, GHT, CHT+GDM, GHT+GDM, PE) had ongoing antihypertensive therapy with oral alpha-methyldopa (Dopegyt, EGIS Pharmaceuticals 105 PLC., Budapest, Hungary) and they had dietary salt restrictions according to the Hungarian guidelines.

6.1.1. Diagnostic criteria for chronic hypertension

Inclusion criteria for chronic hypertension (CHT) was high blood pressure pre-dating pregnancy. As many women did not have their blood pressure measured before pregnancy, we relied on the first trimester blood pressure according to ISSHP when defining high blood pressure in these women.

6.1.2. Diagnostic criteria for gestational hypertension

Inclusion criteria for gestational hypertension (GHT) was new onset of hypertension after 20^{th} weeks of gestation, for which it was important to have normal blood pressure documented

either before pregnancy or at least in early pregnancy before pregnancy-related decrease in blood pressure occurred.

6.1.3. Diagnostic criteria for preeclampsia

In the diagnosis of PE we applied the definition of ISSHP, which defines PE as a combination of new onset of hypertension, that occurs after 20th weeks of gestation and the coexistence of one or more of the following new-onset conditions: proteinuria (spot urine protein/creatinine >30 mg/mmol or >300 mg/day or at least 1 g/L [‘2 + ’] on dipstick testing); maternal organ dysfunctions such as renal insufficiency (creatinine >90 umol/l), liver involvement (elevated transaminases – at least twice upper limit of normal ± right upper quadrant or epigastric abdominal pain), neurological complications (eclampsia, altered mental status, blindness, stroke, hyperreflexia accompanied by clonus, severe headaches accompanied by hyperreflexia, persistent visual scotomata), or hematological complications (thrombocytopenia – platelet count <150 G/l, DIC, or hemolysis); uteroplacental dysfunction in the form of intrauterine growth restriction (IUGR).

6.2. Diagnostic criteria for intrauterine growth restriction

Those fetuses whose estimated weight (EFW) - based on formula B of Hadlock - was below the 10th percentile for their gestational age were considered as a fetus with intrauterin growth restriction (IUGR).

6.3. Diagnostic criteria for gestational diabetes mellitus

GDM was defined on the basis of the recommendation of the World Health Organization (HAPO) 2010: fasting blood glucose level is between 5,1-6,9 mmol/l; or normal fasting glucose, but postprandial 120-minute value is between 8,5-11,0 mmol/l, which correlates with the guideline of the Hungarian College of Obstetricians and Gynecologists.

In our study patients are screened with oral glucose tolerance test (OGTT) containing 75 mg oral carbohydrate. Maternal serum glucose level (sample tube used contained potassium oxalate and sodium fluoride/Na_2 - EDTA) was measured at 0 min. and after 2 hours.

Patients with high risk for GDM were screened with OGTT between 12-16 weeks of gestation, and in case of a negative test result OGTT was automatically repeated between 24-

28 weeks of gestation. In case of low risk for GDM patients were screened between 24-28 weeks of gestation.

6.4. Inclusion criteria

In our study, we analyzed singleton pregnancies between 20-38 weeks of gestation, which were divided into six groups as you can see below. Gestational age was determined on the basis of the first day of the last menstrual period and on the basis of the first trimester ultrasound biometry (biparietal diameter (BPD) and crown-rump length (CRL):

- NBP group of pregnant women with normal blood pressure, (N=109)
- CHT group of pregnant women with chronic hypertension, (N=43)
- CHT+GDM group of pregnant women with chronic hypertension complicated with gestational diabetes mellitus, (N=25)
- GHT group of pregnant women with gestational hypertension, (N=57)
- GHT+GDM group of pregnant women with gestational hypertension complicated with gestational diabetes mellitus, (N=23)
- PE group of pregnant women with pre-eclampsia, (N=17)

Exclusion criteria included multiple pregnancies; enlarged (≥3mm) nuchal translucency from 11+0 to 13+6 weeks of gestation; thrombophilia; molar pregnancy; structural or chromosomal anomaly and fetal abnormalities (with 1 month follow-up after delivery); abnormally invasive placenta; placenta previa; self-reported drug, alcohol, caffeine or nicotine abuse; exposure to circulatory medications (calcium dobesilate, oxerutin); systemic diseases (vasculitis, HIV infection etc.); or not signing the consent form.

6.5. Ultrasound examination

6.5.1. Conventional 2D ultrasound

Examination started with fetal biometry in 2D mode ultrasound to assess biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL) and to calculate estimated fetal weight (EFW) with the help of formula B of Hadlock, followed by color Doppler study of the uterine arteries.

6.5.2. Measurement of uterine artery peak systolic velocity

To identify the uterine arteries, we obtained a sagittal section of the uterus, and used color flow mapping for AUtPSV (cm/s). Then we applied color Doppler with the sampling gate set at 2 mm. The angle of insonation was <30º and we recorded at least three consecutive uniform waveforms. The impact of placentation on AUtPSV was ruled out by calculating the average value of the left and right uterine artery, and pulsatility index (PI) was measured as well.

6.5.3. Volume acquisition

The next step was the 3D scan of the placenta at the insertion point of the umbilical cord. We used 3D rendering mode, in which the color and gray value information was processed and combined to give a 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. As this technique is more sensitive to patient movements, volumes should be acquired while avoiding any probe or patient movements.

The 3D static volume box was placed over the highest villous vascular density zone at umbilical cord insertion. The sweep angle was set at maximum 70°. The three planes of the acquired placental volume were explored to localize the zone where the highest vascular density was found by power Doppler mode. Volume acquisition was made during a time interval varying from 5 to 10 s in the absence of fetal movements and with the mother staying as still as possible. We used fast-low resolution acquisition to avoid any kind of artifacts. The variation in acquisition time was also dependent on the size of the volume box, and it correlated with the age of gestation.

6.5.4. Calculation of 3-dimensional power Doppler indices

We used Mercé-type sono-biopsy, a reproducible, valid alternative for evaluation of the vascular tree of the entire placenta. Volume files were analyzed using the virtual organ computer-aided analysis (VOCAL) software. The spherical sample volume was 28 mL constantly.

The VOCAL software automatically calculated the color scale values in a histogram, and the vascularization indices:

- vascularization index (VI): denotes the ratio of color-coded voxels to all voxels within the volume and is expressed as a percentage,
- flow index (FI): represents the mean power Doppler signal intensity from all color-coded voxels,
- vascularization flow index (VFI): derived from VI and FI through a complex mathematical formula.

The 2D and 3D ultrasound acquisitions were performed at the same time, and 3D volume files were analyzed by VOCAL at a later time. The ultrasound images of 2D and 3D scans were stored on a hard disk (HD).

6.6. Statistical analyses

Statistical analyses were conducted with IBM SPSS Statistics 21.0 for Windows program (IBM, New York, USA). Kolmogorov-Smirnov test results were significant for our database demonstrating that our study samples were not normally distributed. Continuous variables were expressed as median±standard deviation (SD). Kruskal–Wallis tests were used for comparison of continuous variables depending on the groups, whereas comparison between the pathological groups was assessed with Mann–Whitney U test in case of vascularization indices, and with Bartlett's test with Bonferroni's modification in case of AUtPSV, (level of significance was set at $P<0,05$). Univariate comparisons for categorical variables were assessed with $\chi 2$ tests. Linear regression coefficient values and equations depending on gestational age were also calculated for VI, FI, VFI and AUtPSV for all pathological and control groups. Association between placental 3-DPD indices, AUtPSV, 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.

7. Results

Our examinations demonstrated that vascularization indices, and AUtPSV are independent from maternal age and gestational weeks.

7.1. Vascularization indices

Vascularization indices of each groups examined are demonstrated below:

- *VI* (%, median±SD): NBP: 10.4±6.2; CHT: 14.4±10.1; GHT: 7.7±7.1; CHT+GDM: 5.3±3.5; GHT+GDM: 5.4±2.4; PE: 4.9±3. 2;
- *FI* (median±SD): NBP: 46.1±7.6; CHT: 41.5±8.2; GHT: 38.5±9.6; CHT+GDM: 42.8±9.6; GHT+GDM: 36.4±8.3; PE: 36.5±5.7;
- *VFI* (median±SD): NBP: 4.1±2.5; CHT: 3.6±2.8; GHT: 3.0±2.5; CHT+GDM: 2.3±1.5; GHT+GDM: 2.0±1.1; PE: 2.0±1.6.

In case of CHT we found that VI is significantly higher, and FI is significantly lower, while in case of GHT both VI, and FI are significantly lower compared to NBP. In case of PE both VI and FI were found to be significantly lower compared to GHT.

In case of CHT or GHT complicated with GDM significantly lower VI were found compared to NBP, or CHT and GHT alone.

7.2. Uterine artery peak systolic velocity

AUtPSV results of each groups examined are demonstrated below:

- *AUtPSV* (cm/s, median±SD): NBP: 59.5±23.1; CHT: 50.0±16.6; GHT: 56.8±18.4; CHT+GDM: 45.3±14.1; GHT+GDM: 68.6±30.9; PE: 52.4±13.0.

In case of GHT+GDM, AUtPSV was significantly higher compared to NBP and GHT groups.

7.3. Maternal characteristics

The highest mean maternal age was observed in the CHT+GDM group (NBP vs. CHT+GDM: $p=0.023$). We also found increased mean maternal age in case of CHT and GHT+GDM ($p=0.037$) compared to NBP. In case of GHT and PE there was no significant difference in mean maternal age compared to NBP.

Pre-gestational BMI was significantly higher ($p<0.01$) in GHT+GDM (33.46±7.11) compared to GHT (30.37±5.80), as well as in CHT+GDM (32.84±3.64) compared to the CHT (30.55±5.68) group. Mean FI was 45.7 in case of normal pregestational BMI and 41.2 in case of elevated BMI. Elevated pregestational BMI had substantial influence on FI depression ($p=0.048$).

The highest maternal obesity rates were observed in the CHT (58.1%), and the CHT+GDM (60.0%) groups. The lowest cesarean section rate was observed in the NBP group (26.6%). In case of CHT (67.4%) and GHT (64.9%) the rate was markedly increased compared to NBP, but there was no significant difference between the two pathological groups. When pregnancy hypertension was complicated with GDM the cesarean section rate was further increased: CHT+GDM (80.0%), GHT+GDM (95.6%).

7.4. Neonatal characteristics

In the assessment of neonatal outcome rate of apnea, it was significantly higher in GHT patients ($p=0.042$) compared to CHT patients and it was even more elevated in GHT+GDM ($p<0.001$), CHT+GDM ($p<0.001$) and PE ($p=0.001$) cases.

One other characteristic perinatal complication specific to newborns of diabetic mothers, hypoglycemia was also significantly higher in CHT+GDM ($p=0.012$) compared to CHT, and in GHT+GDM ($p=0.022$) when compared to GHT.

Strong positive linear correlation was found between VI ($p=0.009$), FI ($p=0.007$) and neonatal birth weight (BW).

Premature birth rate was the highest in PE. All PE cases were consisted of patients with GHT and IUGR.

Male/female ratio was 32.5%/67.5% in case of CHT, 47.7%/52.3% in case of NBP, 54.3%/45.7% in case of GHT, and 35.3%/64.7% in case of PE.

8. Discussion

Placental vascularization found lower in our 2nd and 3rd trimester *in-vivo* study in case of pregnancy hypertension (CHT, GHT and PE), and the effect of GDM on placental vascularization, and AUtPSV values in pregnancies complicated with pregnancy hypertension (CHT+GDM and GHT+GDM) were also determined.

We should also underline that, our study was the first, that examined the effect of GDM on placental vascularization indices and AUtPSV values in pregnancies complicated with pregnancy hypertension before.

The method is very sensitive and, therefore, we had to reduce the interobserver bias: 1. We had to apply standardized settings of the ultrasound equipment. 2. The same person had to perform all the ultrasound examinations, and collect clinical data. 3. Another person had to analyze the 3-DPD volume files without the awareness of the clinical data. 4. As fetal movements and maternal respiratory movements result in artifacts in the 3-DPD records we had to ask the mother to lay as motionless as possible.

8.1. Placental vascularization indices

Placental vascularization found lower in our 2nd and 3rd trimester *in-vivo* study in case of GHT and PE.

In CHT we can say that, there is significantly lower FI rate, and significantly higher VI rate than in NBP, which clearly describes the nature of placental development in an unfriendly environment of pregnant women predisposed to chronic hypertension. This is a natural defense mechanism from the placenta against the unfriendly hemodynamic conditions. Since the 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.

Our results showed lower VI in pregnancies complicated by GHT and PE compared to NBP group, though the difference was not significant. 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. 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 rather than to CHT. In this case, the fetus mostly develops into an abnormally grown baby. IUGR rate was 22.97% among GHT cases, 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.

8.2. Uterine artery peak systolic velocity

The increased AUtPSV of diabetic women demonstrated in our study may reflect changes in systemic arteriolar placental afterload, myocardial contractility, heart rate and preload. The placenta in diabetic pregnancy has morphological changes that may result in reduced uteroplacental perfusion. The absence of a difference in uterine artery PI values between fetuses of diabetic women and normal controls argues against a modification increased arterial compliance may increase AUtPSV without altering afterload.

8.3. Maternal characteristics

The highest mean maternal age was found in case of pregnancy hypertension complicated with GDM, highlighting the fact that higher maternal age is an important risk factor in GDM. Above it the GDM has effect on neonatal outcome, as well. GDM gives a higher rate for hypoglycemic episodes and feeding difficulties.

The mean gestational age at the time of delivery was the lowest in the PE group as expected. Lower mean gestational age at the time of deliver was found in case of CHT+GDM and GHT+GDM compared to NBP, CHT and GHT, although the difference was not statistically significant, that proves our previous expectation, that gestational diabetes will further worsen placental vascularization.

The highest pre-gestational BMI was found in the groups complicated with GDM, as expected, that shows the effect of increasing mean maternal age. The most patient with BMI over 30 was found in the CHT and CHT+GDM groups.

It is also important to underline, that the amount of weight gain was the highest in groups with the highest adverse pregnancy outcome rates, such as GHT, GHT+GDM, and PE.

8.4. Neonatal characteristics

From the point of view of Apgar scores (1’-5’-10’) no significant differences were found, which suggests, that pregnancy hypertension complicated with pregnancy hypertension influences mainly the intrauterine development of the fetus and the adapting process of the newborn, but not the perinatal events.

Apnea and hypoglycemia mainly occur in pregnancies complicated with gestational diabetes mellitus. The high incidence of RDS in PE suggests, that in case of PE a sudden and severe intrauterine hypoxia develops, that leads to premature delivery.

9. Conclusion

Our goal was to examine placental vascularization in 2nd and 3rd trimester, on etiological basis. We found that certain placental vascularization indices and AUtPSV may indicate on significant differences due to gestational pathology, thus placental vascularization indices and AUtPSV can be useful in the early detection of pregnancies at risk in order to possibly prevent complications.

From my point of view the measurement of placental vascularization indices is a useful tool in risk prediction, differential diagnosis, and determining anti-hypertensive therapy effectivity, while uterine artery peak systolic velocity helps to find pregnant women at risk for gestational diabetes mellitus earlier.

10. New statements

1. There is significant difference in 3-DPD placental vascularisation indices, between case group of pregnancy hypertension and control group of normal blood pressure pregnancies.
2. There is significant difference in 3-DPD placental vascularisation indices, between pathological groups of chronic-, gestational hypertension and preeclampsia.
3. There is negative correlation between placental 3-DPD vascularization indices and the severity of pregnancy hypertension case.
4. There are significant differences in 3-DPD placental vascularization indices and maternal characteristics among pregnancy hypertension types (CHT, GHT and PE).
5. There are significant differences in 3-DPD placental vascularization indices and fetal characteristics among pregnancy hypertension types (CHT, GHT and PE).
6. There are significant differences in 3-DPD placental vascularization indices and neonatal characteristics among pregnancy hypertension types (CHT, GHT and PE).
7. There is negative correlation between placental 3-DPD vascularization indices and adverse pregnancy outcome rates.
8. The placental 3-DPD vascularization indices show gradual decrease trough pregnancy.
9. There is negative correlation between placental 3-DPD vascularization indices and
10. The value of uterine artery peak systolic velocity is increased in case of pregnancy hypertension when complicated with gestational diabetes mellitus.
11. There is negative correlation between placental 3-DPD indices and the severity of histological finding of the placenta in case of pregnancy hypertension.
12. The measurement of placental 3-DPD vascularization indices with the help of VOCAL software in second a third trimester, in case of pregnancy hypertension (chronic- (CHT), gestational hypertension (GHT) or pre-eclampsia (PE)) can be a useful screening method in the prevention of complications.
13. The measurement of uterine artery peak systolic velocity (AUtPSV) can be a useful method of screening gestational diabetes mellitus (GDM).