EXAMINATIONS OF PLACENTAL THREE-DIMENSIONAL POWER DOPPLER INDICES IN PREGNANCIES COMPLICATED BY DIABETES MELLITUS AND INTRAUTERINE GROWTH RESTRICTION

Summary of Ph.D. Thesis

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1. List of publications

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2. Abbreviations:

2-D	two dimensional
2-DPD	two-dimensional power Doppler
2-DCD	two-dimensional color Doppler
3-D	three-dimensional
3-DPD	three-dimensional power Doppler
ACOG	American College of Obstetrics and Gynecology
AD	abdominal diameter
AOR	adjusted odds ratio
BMI	body mass index (kg/m^2)
CI	confidence interval
D	the minimum telediastolic velocity (cm/s)
FI	flow index
GA	gestational age
GDM	gestational diabetes mellitus
HIV	human immunodeficiency virus
IUGR	intrauterine growth restriction
OGTT	oral glucose tolerance test
PD	power Doppler
GDM	gestational diabetes mellitus
Na_2EDTA	natrium ethynildiamintetraacetat
PI	pulsatily index
RI	resistance index
S	the maximum systolic velocity (cm/s)
T1DM	diabetes mellitus type I
VOCAL	virtual organ computer-aided analysis
VFI	vascularisation flow index
VI	vascularisation index (%)
vs	versus
WHO	World Health Organisation

3. Introduction

The placenta has several important roles: divides the foetal and the maternal circulation, supplies the developing foetus with nutrients and oxygen, functions as an endocrine organ and filters the excreta. Therefore, the adequate vascularisation of the placenta is very important for the intrauterine physiologic development of the foetus. An increased resistance of the pathological foeto-maternal circulation can lead to an insufficient circulation and function of the placenta, which can result a reduced oxygen supply of the foetus. Therefore maternal diseases such as diabetes, which result vascular diseases and thus have an effect on the condition of the uteroplacental circulation. Therefore they have an effect on the nutrients supply and the development of the foetus, which can be followed-up by measuring the placental circulation.

Conventional two-dimensional (2-D) ultrasound has been widely used for the evaluation of the placenta during pregnancy. This 2-D ultrasound evaluation includes the morphology, anatomy, location, implantation, anomaly, size, and color/power and pulsed Doppler ultrasound assessment of the placenta. The 2-D ultrasound is useful to assess normal and abnormal placentae in most pregnancies. The three-dimensional (3-D) reconstruction of the placenta gives information about 3-D placental vasculature and placental blood flow, 3-D power Doppler ultrasound as well as quantitative 3-DPD histogram analysis by Virtual Organ Computer-aided Analysis (VOCAL) program, quantitative and qualitative assessments of the the vascularisation and blood flow of the placenta. 3-DPD ultrasound can depict intraplacental vessels characteristics such as the coiling of vessels, branching and caliber changes by subjective. We analysed the alteration in vascularisation by objective with VOCAL program.
Nowadays, the prevalence of the pregnancies complicated by intrauterine growth restriction (IUGR) and diabetes mellitus shows an increasing tendency, therefore the role of the ultrasound examination is pronounced in the diagnosis of the pathological pregnancies, follow-up and in the restriction of the occurrence of perinatal morbidity and mortality.

In our prospective study placental vascularisation was measured by 3-DPD technique and VOCAL program in normal and pathological (diabetes mellitus (GDM/T1DM) and IUGR) pregnancies.

A consecutive series of pregnant women was recruited for our study at the Outpatient Department of Obstetrics and Gynecology, University of Szeged, between 2011 and 2013.

4. Aims of the investigation

The aims of our study were:

I. GDM/T1DM

1. To evaluate the placental 3-DPD indices in pregnancies complicated by the alteration of carbohydrate metabolism (GDM and T1DM pregnancies) in the second and third trimester.
2. Observe the changes of 3-DPD indices by gestational age.
3. We tested the hypothesis that there is an association between umbilical/uterine artery flow 2-D color Doppler indices (2-DCD) and placental 3-DPD indices both in T1DM and GDM as well as in the control group.

II. IUGR

1. To evaluate the placental 3-DPD indices in pregnancies complicated by IUGR in the second and third trimester.
2. To analyze the correlation between conventional uterine/umbilical artery flow 2-DCD indices and 3-DPD indices in pregnancies complicated by IUGR.
3. The effect of parity, gravidity and pregestational BMI to the alteration of vascularisation indices.
4. To examine perinatal outcomes in pregnancies complicated by IUGR.

5. Material and methods:

5.1. Diagnosis of GDM/T1DM

Diagnostic criteria for DM and GDM are based on World Health Organisation's guide (WHO), which correlates with guide of Hungarian College of Obstetrics and Gynecology. In our study oral glucose tolerance test (OGTT) was used between 24-28th weeks of gestation to diagnose diabetes: 75 grams of glucose solution was consumed by the pregnant woman after an 8 hours fasting period. OGTT was applied as a screening and diagnostic test for diabetes.

The glucose level in maternal serum (sample tube contains potassium oxalate and sodium fluoride/Na_2 EDTA) samples was measured at the start (0 min) and after 2 hours.

Diagnostic criteria for GDM are set up, if:

a) the fasting blood glucose level is ≥ 7 mmol/l, or

b) the fasting glucose is normal, but the postprandial 120-minute value is ≥7.8 mmol/l, or

c) the random glucose level is ≥11.1 mmol/l which are measured in different time. If women before subsequent pregnancy had been affected by DM, the OGTT was not performed, but dietary treatment was administered.

High risk pregnancies for GDM were screened with OGTT between 12-16 weeks of gestation, and if the result was below the limit, then OGTT was repeated between 24-28 weeks of gestation. In our country the patients who do not have high risk for GDM are screened with OGTT when they are 24-28 weeks pregnant.

5.2. Diagnosis of IUGR

A fetus whose estimated weight is below the 10^{th} percentil of the standard age and sex is considered growth restricted (IUGR).

5.1.1. GDM/T1DM

The pregnancies were divided into two groups: I. non-pathological control group (n=113) and II. case group comprising pregnancies complicated by two subgroups of diabetes mellitus (n=99): II.a) T1DM (n=43) and II.b) GDM (n=56). Exclusion criterias are: multiple pregnancy, enlarged (≥3mm) nuchal translucency from 11^{+0} to 13^{+6} weeks of gestation, fetal or neonatal structural or chromosomal anomaly, inadequate localization of the placenta (placenta praevia), posterior placenta, self-reported drugs, alcohol, caffeine or nicotine abuse, exposure to circulatory medication (oxerutins, calcium dobesilate), not signing the consent form. Diabetes accompanied by another systemic disease (autoimmune disease, vasculitis, haemophylia, thrombophylia, HIV infection, etc.), abnormal HgA1C value.

5.2.1. IUGR

The pregnancies were divided into two groups: non-pathological control group (n=171) and IUGR group (n=52).The excusion criterias are same as in GDM/T1DM study except for posterior wall placenta and complete with diabetes mellitus.

5.3. Conventional two-dimensional (2-D) and color Doppler investigations

The determination of GA was based on the first day of the last menstrual period and/or on ultrasound biometry (crown-rump length and biparietal diameter) at 10^{th} week of

pregnancy. If the difference is more than 10 days, the determination was based on ultrasound calculation. All patients were scanned in a semirecumbent position. An initial 2-D conventional study provided data about fetal position and presentation, body movements, placental localization and umbilical cord insertion. The factorial default setting "Obstetrics/2-3 trimester" was used in 2-D mode. The examination was followed by a fetal biometry to assess biparietal diameter, head circumference, abdominal circumference and femur length. Fetal weight was calculated by US machine according to formula B of Hadlock. A conventional color Doppler study of umbilical and uterine arteries were also performed and the flow S/D ratio and resistance index (RI) were calculated according to the formula RI=S–D/S, where S is the maximum systolic velocity and D is the minimum telediastolic velocity. Besides, we measured the pulsatility index (PI) with the help of the formula: PI=S-D/mean velocity. The indices were read from the reports of the display of ultrasound machine.

5.4. Three –dimensional (3-D) ultrasound evaluation of the placenta

3-DPD ultrasound as well as quantitative 3-DPD histogram analysis, quantitative and qualitative assessments of the vascularization and blood flow of the placenta have become feasible.

5.4.1. Three-dimensional power Doppler (3-DPD) ultrasound

3-DPD ultrasound can depict intraplacental vessel characteristics such as the density of vessels, branching and caliber changes. 3-DPD ultrasound was found to be superior to 2-D power Doppler (2-DPD) ultrasound for the detection of secondary and tertiary stem vessels in the placenta by subjective mode.

5.4.2. Quantitative three-dimensional power Doppler (3-DPD) histogram analysis

3-D volume is constituted of small units of volume-„voxels”. Voxels contain all the information about grey-scale and color, according to an intensity scale ranging from 0- to 100. According to these values, this measure system obtains 3-DPD indices to evaluate vessels and blood flow.

a, vascularisation index (VI), which refers to the color voxel/total voel ratio, measures the number of color voxels in the sudied volume, which represent the blood vessels within the volume of interest, and expresses it as a percentage (vascularity).

b, flow index (FI) is the average color value of all the color voxels and it shows the average blood flow intensity from 0 to 100 (placental blood flow, no unit).

c, vascularization flow index (VFI), which refers to the weighted colour voxel/total voxel ratio, combining the information on vessel presence (vascularity) and amount of blood cells transported (blood flow, no unit). The value is 0-100.

The VOCAL program automatically calculates gray-scale and color values (VI, FI, and VFI) from the acquired sample.

5.5. Volume acquisition

Acquisition of the images used for the determination of placental volume and 3-DPD indices were obtained at the time of visit. Each sample was examined using 3-D rendering mode, in which the color and gray value information was processed and combined to give 3-D 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). For laterally located placentas slight lateral inclination of the transducer was positioned to obtain proper images. 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. We used fast low resolution acquisition to avoid any kind of artifacts. The 3-D static volume box was placed over the highest villous vascular density zone at umbilical cord insertion. The sweep angle was set at maximum 70 degrees. Volume acquisition was made during a time interval varying from 5 to 15 seconds in the absence of fetal movements and with mother being as motionless as possible.

5.6. Calculation of power Doppler (PD) Indices

The stored volumes were further analyzed using VOCAL program by an expert in 3-D analysis. Each volume was recovered from the hard disk in succession and processed using the multiplanar system. The type of sonobiopsy (called “Merce-type sonobiopsy”) that we used is a reproducible, validated method and by obtaining a representative sample of the placental tree it is applicable throughout the whole pregnancy in contrary to other methods, in which the entire placenta needs to be visualized.

5.7. Statistics

5.7.1. Statistical analysis methods in groups GDM/T1DM

The statistical analysis was conducted with SPSS for Windows version 17.0 (SPSS Inc, Chicago, IL, USA). The continuous variables were expressed as median±standard deviation. Kruskal-Wallis tests were used for comparison of continuous variables depending on the three subgroups (T1DM versus (vs.) GDM vs. controls), whereas comparison between two subgroups (T1DM vs. GDM) was assessed with Mann-Whitney-U test. Univariate comparisons for categorical variables were assessed by $\chi 2$-tests. Linear regression coefficient values and equations depending on gestational age were also calculated for VI, FI, VFI indices both for diabetic and control groups. The distributions of placental indices (25th, 50th and 75th centiles) according to GA were plotted and predictive values were also calculated for diabetic pregnancies. The association between placental 3-D power Doppler indices and 2-DCD indices (RI and PI of umbilical and uterine arteries) was determined by Spearman's rank correlations.

5.7.2. Statistical analysis methods in group IUGR

The statistical analysis was conducted with SPSS for Windows version 17.0 (SPSS Inc, Chicago, IL, USA). An analysis of variance (ANOVA) was carried out to examine the association of the 3DPD indices with the gravidity, parity, and pregestational body mass index (BMI). The Mann–Whitney *U* test, the *t* test, and the z-score were used to compare 3-DPD indices (VI, FI, VFI); estimated fetal weight, birth weight, and birth length; the mode of delivery; the occurrence of intrauterine complications; the necessity of transfer to the neonatal intensive care unit; the Apgar scores at 1, 5, and 10 minutes; and the umbilical cord arterial pH between the IUGR group and the control group. $p \leq 0.01$ was considered statistically significant. A quantile regression method was used to investigate the relationship between 3-DPD indices (VI, FI, VFI) and gravidity, parity, and pregestational BMI. The association between placental 3-D power Doppler indices and 2-DCD indices (RI and PI of umbilical and uterine arteries) was determined by Spearman's rank correlations.

6. Results

6.1. GDM/T1DM

The characteristics of pregnancies are [GDM (n=56), T1DM (n=43), control (n=113)]: maternal age (years)(mean±S.D.): [GDM (33±5.1), T1DM (32±5), control (30.7±5.4)], weeks of gestation (mean±S.D.): [GDM (30^{+7}±6^{+4}), T1DM (31 ±7^{+4}), control (28^{+4} ±5^{+5})], estimated fetal weight (gram) (mean±S.D.): [GDM (1723±1007), T1DM (1737±1222), control (1223±195.1)]. They show no significant difference in groups control, T1DM and GDM by Kruskal-Wallis test (p>0.05). The ultrasound-derived estimated fetal weight was not distinguishable between the two diabetic subgroups in any logistic regression analysis in relation to GA and placental 3-DPD indices (p>0.05).

The placental vacularisation parameters were the next indices in the study groups: VI (mean±S.D.): [GDM (5.30±3.88), T1DM (4.81±3.72), control (10.26±6.73), p<0.001], FI (mean±S.D.): [GDM (36.71±7.18), T1DM (36.86±10.44), control (44.83±8.47), p<0.001], VFI (mean±S.D.): [GDM (2.12±1.58), T1DM (2.02±1.87), control (4.94±3.73), p<0.001)]. Kruskal-Wallis tests showed that all three placental indices were significantly reduced among diabetic pregnant women as compared to the control group (p<0.001) for each indices. None of placental indices indicated significant difference between T1DM and GDM pregnancies (p>0.05). Multiple logistic regression analysis showed that the odds of GDM are increased at a higher GA [p<0.001, adjusted odds ratio (AOR): 1.1 (95% Confidence Interval (CI):1.07-1.16)] and a lower FI [p<0.001, AOR: 0.88 (95%CI: 0.85-0.93)], or at a higher GA and a lower VI [p<0.001, AOR: 0.83 (95%CI: 0.77-0.94)], or at a higher GA and a lower VFI [p<0.001, AOR: 0.63 (95%CI: 0.51-0.77)]. If all 3-DPD indices are low [FI: p<0.001, AOR: 0.91 (95% CI: 0.87-0.94)]; [VFI: p<0.001, AOR: 0.64 (95% CI: 0.55-0.75)]; [VI: p<0.001, AOR: 0.83 (95% CI: 0.77-0.89)] during late pregnancy, then the odds of the fact that the pregnancy is complicated by any type of diabetes [p<0.001, AOR: 1.10 (95% CI: 1.06-1.14)] is also significantly high.

The placental 3-DPD indices in relation to gestational age in the control group versus diabetic cases. The linear regression equations for VI, FI, and VFI vs. GA among the control cases were as follows: FI=47.82+(-0.13*GA); r=0.123, p<0.001; VI=14.67+(-0.20*GA); r=0.288, p<0.001; VFI=7.44+(-0.11*GA); r=0.233, p<0.001. All 3-DPD indices decreased slightly by gestational age, but it is a constant value during the pregnancy matematically. The linear regression equations were FI=43.41+(-0.23*GA); r=0.182, p=0.07; VI=6.93+(-

0.06*GA); r=0.012, p<0.25; VFI=3.24+(-0.04*GA); r=0.164, p=0.107 among diabetic pregnant women.

The equations were not significantly different from each other in T1DM and GDM group and the parameters of equations were significantly different from the parameters of the control group.

There were no associations between placental 3-DPD indices and 2-DCD indices (RI and PI of umbilical and uterine arteries) which were determined by Spearman's rank correlations (p<0.01).

6.2. IUGR

Demographic and obstetric characteristics were investigated [control (n=171), IUGR (n=52). Placental location [(control: anterior wall: 97 (56.7%), p=0.23; posterior wall: 74 (43.3%), p=0.22) vs. (IUGR: anterior wall: 29 (55.8), p=0.23 posterior wall: 23 (44.2) p=0.22)] and 1-minute Apgar score (mean ± SD) [control (8.9 ± 2.3) vs. IUGR (9.0 ± 1.4) p=0.12]) did not differ significantly between groups. Gravidity [control: < 3: 123 (71.9%), ≥3: 48 (28.1%) vs. IUGR: (<3: 28 (53.8%), ≥3: 24 (46.1%), p=0.01)], parity [control: (< 3: 87 (83.6%), ≥3: 17 (16.4%) vs. IUGR: (<3: 26 (76.4%), ≥3: 8 (13.6%), p=0.01)], pregestational BMI (mean ± SD.) [control (22.1 ± 2.5) vs. (IUGR: (21.9 ± 1.5), p=0.01], umbilical cord artery pH (mean ± SD): [control (7.2 ± 0.2) vs. IUGR (6.9 ± 1.6), p=0.01.], and 5-minute and 10-minute Apgar scores (mean ± SD.): [control (9.3 ± 1.3; 9.5 ± 0.8) vs. IUGR: (9.7 ± 0.9; 9.8 ± 1.0), p=0.01] did differ significantly.

Women in the IUGR group had significantly lower 3-DPD indices (VI, FI, VFI) values than did the control group [VI (median (interquartile range) (%): control: 10.1 (8.6-10.9) vs. IUGR: 3.7 (3.2-4.2), p=0.001; FI (median (interquartile range)): control: 45.1 (44.1-53.1) vs. IUGR: 40,0 (39.7-42.5), p=0.0012; VFI (median (interquartile range)): control: 4.8 (4.4-5.3) vs. IUGR: 2.2 (2.1-2.4), p=0.0001]. We compared the vascularization indices among women with different gravidities, parities, and pregestational BMIs. Gravidity, parity, and pregestational BMI had no significant effect on VI, FI, VFI by quantile regression analyses (p>0.01), but there were significant differences in VI, FI, VFI between the control and IUGR groups (p<0.01).

Perinatal complications occurred among 12 (23.1%) neonates in the IUGR group and 12 (7.0%) in the control group (p=0.01). Neonatal intensive care was needed for 16 (30.8%) infants in the IUGR group and 13 (7.6%) in the control group (p=0.01). Median length of

pregnancy was 38.4 weeks (interquartile range 37.3–39.1) in the study group and 39.1 weeks (interquartile range 38.1–40.0; p=0.2) in control group. The mean birth weight was 2674.4 ± 752.1 g in the study group and 3351.9 ± 522.4 g in the control group (p=0.01). The mean birth length was 46.5 ± 3.4 cm in the study group and 49.6 ± 2.45 cm in the control group (p=0.01). The mean z-score for the estimated fetal weight in IUGR pregnancies measured from 30 to 38 weeks of pregnancy was –2.9, indicating that the estimated fetal weights in the IUGR group were below the average measured in the control group by nearly three times the standard deviation. There were no associations between placental 3-DPD indices and 2-DCD indices (RI and PI of umbilical and uterine arteries) which were determined by Spearman's rank correlations (p<0.01).

7. Discussion

7.1. GDM/T1DM

We found no correlation between 3-DPD indices and GA in normal pregnancies. The VI, FI and VFI indices are contant during the pregnancy A declining tendency of 3-DPD indices was remarkable in diabetic pregnancies. The control group and the diabetic groups had overlaps of VI, FI, VFI values; hence 3-D power Doppler indices are not diagnostic in diabetes. The quantitative changes in the vascular tree in the placenta in pregnancies complicated by T1DM/GDM are not well defined. Decreased placental VI, VFI in diabetes could be associated with down-regulated angiogenesis, diminished number of arterioles and the hypertrophic wall of these vessels. The depressed FI might represent narrower inner vascular diameter.

The distinct placental changes associated with diabetes mellitus depend on the gestational period. In the early pregnancy the high glucose level triggers vasculogenesis, but vasculopathy is not present yet. In later stage of pregnancy the vasculopathy destroys the blood flow in placenta, especially in poor glycaemic control. Reasons for reduced placental blood flow (FI) in diabetes are: inadequate opening of spiral arteries, acute atherosis, reduction in intervillous space volume because of villus oedema and more bulbous villi. GDM correlates to diminished branching, attenuated coiling, mitigated vascular diameters. The alteration of placental vasculature leads to diminished function of placenta. Since in T1DM/GDM the volume and weight of placenta increases (the placental parenchymal and villous tissue content is higher than in non-diabetic normal pregnancies), VI is proportionally reduced scaled to volume unit.

The uteroplacental circulation can be detected by flowmetry of the umbilical and uterine arteries. Our study confirms the results of other research groups referring to their statements that GDM does not induce changes in umbilical and uterine circulation. In diabetes, increased blood flow resistance of the umbilical artery is just a late pathognomic sign of ischemic vascular changes in placenta, therefore we added the analysis of the placental microcirculation to the conventional indirect uteroplacental sonographic examination.

The "Merce-type sonobiopsy" was applied in our study as a well-defined, validated method, in which both the intraobserver and interobserver errors are low. This method can be used not only in the first trimester, when the overwhelming majority of the abnormalities in high-risk pregnancies has not been developed yet, but also in the second and third trimester.

The studies about reproducibility demonstrated that the measurement of placental microcirculation by sonobiopsy can be appropriate for opting for measuring placental indices for a long time-period (between 10 and 41 weeks of gestation). The umbilical cord insertion can be visualized until the end of pregnancy. From the early second trimester on it is impossible to visualize the placenta completely on the posterior wall that is why we excluded the cases with posterior placenta. In addition, the growth of the fetal skeleton reduces the effect of ultrasound examination.

Pregnant women with DM in our study did not have any other microvascular diseases such as retinopathy or nephropathy, though fetal vessels of placenta showed dramatic changes in VI, FI and VFI. This assumes, that placental microvasularisation in diabetes is under control of fetal circulation factors as well.

In our study, only the most vascularised placental region (the region at of umbilical cord insertion) was measured correlated to a standard volume unit. We applied sonobiopsy as the most accurate measurement method concerning vascularisation. Placental 3-DPD indices, measured by sonobiopsy clearly point to a decreasing tendency in regard to increasing GA in diabetic mothers. In addition, our measurements demonstrate that the placental region close to the umbilical cord insertion has constant vascularisation during normal pregnancy, which deteriorates decreased by the impaired glucose metabolism. However, significant difference can not be observed between cases when diabetes has been developed prior to and during mid as well as late pregnancy.

7.2. IUGR

The women with an IUGR pregnancy and those in the control group did not differ

significantly in terms of maternal age, pregnancy duration at the time of the examination, 1-minute Apgar scores and placental localization. This finding indicates that these factors had no influence on the condition of the arteries or the extent of angiogenesis during pregnancy.

The frequency of cesarean delivery was significantly higher among women with an IUGR pregnancy than in the control group.

Apgar scores decreased with decreasing values for all 3-DPD indices, but the 5-minute and 10-minute Apgar scores showed significant differences with regard to VI, FI, and VFI, which can be explained by poor postnatal adaptation of infants who had been growth-restricted in the uterus. Complications such as hypothermia, hypoglycemia, polycythemia, hyperviscosity, and breathing problems emerged, and neonatal intensive care was necessary more often in IUGR cases. The decrease in all three 3-DPD indices was significant. The VFI was the most sensitive predictor of complications. However, we recommend use of the FI to screen for IUGR pregnancies at increased risk of perinatal complications because this parameter is minimally influenced by other factors, such as equipment settings. The FI has the lowest coefficient of variation and the lowest rate of intraobserver/interobserver errors of the three vascularization indices.

The study confirms our hypothesis that the placental location has no significant influence on the three placental vascularization indices. In the present study, women with placental adhesion anomalies and morphological disorders were excluded because such pregnancies can be affected by insufficient circulation from the beginning of the pregnancy and this could have influenced the findings.

8. Conclusion

A significant reduction in placental 3-DPD indices could be measured in pathological pregnancies (diabetic and growth restricted) applying the 3-D sonobiopsy, which is a valid alternative for evaluation of the placental vascular tree when visualization of the entire placenta is not feasible. The evaluation of altered placental vascularisation by measurement of 3-DPD indices (VI, FI, VFI) could be useful in checking the pathological pregnancies, however further studies on association between other pregnancy characteristics and 3-DPD indices are necessary in order to evaluate the usefulness of this method in screening complications of pathological pregnancies.

In the future we would like to continue our research on this method, to develop and promote the accessibility of this method in clinical centres, but later in county hospitals as

future screening centres as well and to make the possibilities of conventional identification of risk-pregnancies complete. Therefore we can affirm with certainty that after the evaluation of the findings and the adaptation of this method to the routine screening practice, we would improve the perinatal outcomes regarding morbidity and mortality. Our study group wishes to contribute to the creation of these potential facilities and I hope that based upon our research results this screening method will once become part of the pregnancy-care protocol. If we had the opportunity to accomplish this method in Hungary, we would be pioneers in the methodology and quality level of pregnancy care in Central and Eastern Europe.