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Early Prediction of Preeclampsia and Intra Uterine Growth Restriction

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Summary

In the introduction (CHAPTER 1) an overview of relevant predictive markers for preeclampsia and intra uterine growth restriction is described. CHAPTER 2 focuses on reproducibility of three-dimensional ultrasound measurements and in CHAPTER 3 the clinical use of sonographic fetal and placental volumes measurements is reviewed. CHAPTER 4 describes the relationship of spiral and uterine artery Doppler measurements and in CHAPTER 5 the predictive value of spiral arteries Doppler measurements for adverse pregnancy outcome is assessed. In CHAPTER 6 AND 7 maternal serum markers A Disintegrin And Metalloprotease 12-s (ADAM12s), placental protein 13 (PP13) and metastin are evaluated for their predictive value for preeclampsia (PE), pregnancy-induced hypertension (PIH) and intra uterine growth restriction (IUGR). According to the criteria of the International Society for the Study of Hypertension in Pregnancy 2001, cases of pregnancy-induced hypertension (PIH) were identified. Pregnancy-induced hypertension was defined as two recordings of diastolic blood pressure above 90 mmHg at least 4 hours apart in a previously normotensive woman. The same criteria were used to identify cases of preeclampsia, defined as pregnancy-induced hypertension combined with proteinuria exceeding 300 mg/24 h or two readings of at least 2+ by dipstick on urinalysis after 20 weeks of gestation.²² Intra uterine growth restriction was defined as birth weight below the tenth percentile, customized by gestational age.

In CHAPTER 2 we assessed the reproducibility of three-dimensional ultrasound (3DUS) measurements of fetal and placental volumes in week 11 till 18 of gestation in a group of 34 uncomplicated pregnancies. Two operators independently acquired fetal and placental volumes using 3DUS. Each placental or fetal volume was acquired twice. Intra- and interobserver reproducibility was expressed in intra- and interclass correlation coefficients (intra-cc and inter-cc). In addition, the effect of individual volume acquisition and caliper placement was evaluated.

Fetal and placental volume measurements were successful in 97% of all cases and the volumes were similar to previous reported literature. The intraobserver reproducibility was good for fetus (intra-cc: 0.99; 0.99) and placenta (intra-cc: 0.99; 0.98). Also, interobserver reproducibility was good for fetus (inter-cc 0.98) and placenta (inter-cc 0.98). In addition, regardless of the operator who acquired the volumes, inter-cc remained good for both fetus (inter-cc: 0.99; 0.99) and placenta (inter-cc: 0.97; 0.99).

Therefore, we concluded that intra- and interobserver variability of fetal and placental volume measurements are low and reproducibility is very good. In addition, we have shown that individual volume acquisition and caliper placement has no significant effect on the calculation of three-dimensional fetal and placental volume measurements.

In **CHAPTER 3** the clinical use of 3DUS measurements of placenta and fetal volume is reviewed. Three-dimensional ultrasound fetal volume measurements are based on head-and-trunk volumes, they are highly reproducible and seem very accurate in assessing fetal weight and monitor fetal growth. However, fetal volume measurements are limited by gestational age, since late second and third trimester fetuses usually exceed the size of the volume box. The clinical value of first trimester measurements is yet to be determined, but significant decreased fetal volumes have been reported in aneuploid fetuses.

Placental volumes measurements are also highly reproducible and easily acquired by 3DUS. Like fetal volumes, these placental volume measurements are limited by gestational age. Literature reports significantly smaller placental volumes in aneuploid fetuses, such as trisomy 13, 18 and 21, although its predictive value seems limited and addition of first trimester placental volume measurements to the current screening tests for aneuploid fetuses shows no improvement in detection rates. The relationship between second trimester placental volume and pregnancies complicated by hypertensive disorders or SGA-fetus seems more promising, although its predictive values are limited by the large heterogeneity in placental growth and size.

Further research for the assessment of predictive values of first trimester fetal and placental volume measurements is warranted.

CHAPTER 4 reports the longitudinal relationship between Doppler flow velocity waveforms of the spiral artery (SA) and uterine artery (UA) in pregnant women. In this study, we analyzed 97 primigravidas with uncomplicated singleton pregnancies. In each pregnancy, SA and combined UA velocity waveforms were assessed using transabdominal ultrasound Color Doppler between gestational weeks 11 through 14, 14 through 18 and 18 through 24. Each Doppler measurement was performed twice. The combined UA was derived from the average pulsatility index (PI) of the left and right UA. In addition, the presence of UA bilateral notching was reported. In total, 284 UA and 263 SA Doppler flow measurements were analyzed. Results showed a continuous decrease of mean PI in SA and UA with increasing gestational age and UA bilateral notching was reported in 35%, 9% and 3% of the cases be-

tween gestational weeks 11 through 14, 14 through 18 and 18 through 24 respectively. Intra observer variability for SA and combined UA was 0.54 and 0.90 respectively. Generalized Estimating Equations analysis showed significant correlation ($r = 0.41$) between SA and UA ($p < 0.0001$).

Our longitudinal data shows that the generally assumed relationship between uterine and spiral arteries Doppler measurements is confirmed and a significant correlation between these measurements is demonstrated; UA Doppler measurements in early pregnancy seem to accurately reflect peripheral resistance of spiral arteries. Furthermore, this study shows that trophoblastic invasion seems a continuous process in the first half of pregnancy in which first trimester bilateral notching probably is a physiological phenomenon.

In CHAPTER 5 we evaluated the longitudinal relationship between SA Doppler measurement and pregnancies complicated by pregnancy-induced hypertension (PIH) or preeclampsia (PE), and intra uterine growth restricted (IUGR) fetuses in 108 pregnant women.

In all pregnancies SA blood flows were measured three times using Color Doppler ultrasound. Measurement were performed between 11 and 14 week, between 14 and 18 weeks and between 18 and 24 weeks of gestation, each measurement was performed twice. Spiral artery blood flows over time were analyzed with multilevel modeling and reference ranges were constructed. Mann-Whitney tests were used to compare uncomplicated and complicated pregnancies. We analyzed 86 uncomplicated pregnancies and 21 complicated pregnancies (4 pregnancies complicated by PE, 7 complicated by PIH and 10 complicated by isolated IUGR).

In the uncomplicated pregnancies, systolic/diastolic (SD-) ratios, resistance index (RI) as well as pulsatility index (PI) decreased progressively with advancing gestational age. Linear regression analysis showed that mean predicted SD-ratio decreased from 1.75 at 11 weeks of gestation (P5 – P95: 1.32 – 2.17) to 1.48 at 24 weeks of gestation (P5 – P95: 1.05 – 1.90). The predicted RI en PI showed similar decrement: mean RI from 0.44 (P5 – P95: 0.28 – 0.59) at 11 weeks of gestation to 0.34 (P5 – P95: 0.19 – 0.50) at 24 weeks of gestation, mean PI from 0.59 (P5 – P95: 0.32 – 0.85) at 11 weeks of gestation to 0.40 (P5 – P95: 0.14 – 0.66) at 24 weeks of gestation. These results are consistent with previously reported literature. The Mann-Whitney tests showed no differences in PI, RI or SD-ratio in pregnancies with growth-restricted fetuses or complicated by preeclampsia. However, a significantly lower RI, PI and SD-ratio were found preclinically in pregnancies complicated by PIH.

In conclusion, these results showed that SA Doppler measurements decrease progressively with advancing gestational age, but the reference ranges are wide. Therefore, SA Doppler measurements are probably not useful for early prediction of PE or IUGR. Decreased Doppler indices preceding PIH are likely caused by a hyperdynamic circulation in women with increased Body Mass Index and (unmasked) pre-existent hypertension.

In CHAPTER 6, maternal serum markers ADAM12S and PP13 were evaluated for their first trimester predictive performance for adverse pregnancy outcome. A retrospective case-control study of samples taken between 2004-2007 was conducted and 55 cases of pregnancies complicated by PE ($n = 17$), PIH ($n = 30$) or isolated IUGR fetuses ($n = 8$) were matched with 165 uncomplicated control cases. The cases were matched for exact gestational age and maternal age with three control cases. In addition, known confounders such as ethnicity, primigravida, smoking and maternal weight were analyzed. The serum concentration of ADAM12S and PP13 were analyzed 'blind' to outcome and results were expressed in multiples of the median (MOM). There was not a normal distribution of ADAM12S and PP13 serum levels, therefore MOM values were compared using Mann-Whitney U test. In addition, receiver-operator-characteristics (ROC) curves were used to assess screening performance.

Results showed significantly reduced median ADAM12S concentrations for controls versus all cases: 405 vs. 324 nG/L (MOM 1.00 vs 0.80 ($p < 0.05$)). In PP13 no significant difference was found between controls and cases; 57.7 vs. 54.6 pG/L (MOM 1.00 and 0.95). Multivariate analysis for possible dependency between ADAM12S and PP13 showed found very weak or no correlation between both markers in the controls or in each group of cases.

Median MOM levels for ADAM12S were 0.90, 0.77 and 0.88 for PE, PIH and IUGR respectively; MOM levels for PP13 were 0.77, 0.95 and 0.89 respectively. ROC analysis yielded areas under the curve (AUC) for ADAM12S and PP13 of 0.63 and 0.59 for PE, 0.68 and 0.57 for PIH and 0.59 and 0.62 for IUGR, respectively. Combined ADAM12 and PP13 did not improve AUC. If specificity was set at 0.80, the corresponding sensitivity of ADAM12S was 52% for PIH.

This study demonstrated that ADAM12S was significantly associated with pregnancies complicated by PIH, although predictive value was limited. Decreased levels of PP13 were not significantly correlated with adverse pregnancy outcome. Combining ADAM12S and PP13 did not appear to improve screening performance.

In CHAPTER 7 we assessed the association between first trimester plasma levels of metastin and small for gestational age (SGA) neonates, defined as customized birth weight below the 10th percentile. Maternal plasma was obtained between week 8 till 14 weeks of gestation and levels of metastin were measured. Thirty-one cases of pregnancies with SGA-neonates were matched with 31 pregnancies without SGA-neonates for gestational age at venipuncture. Measurements of β -hCG were included to study the influence of gestational age and placental volume on plasma levels of the measured marker. Results showed significantly lower metastin levels in SGA-pregnancies compared to the uneventful pregnancies (metastin: 1376 ± 1317 pmol/L vs 2035 ± 1260 pmol/L, $p = 0.035$), β -hCG levels were not significantly different.

Therefore, we concluded that metastin might be useful in combination with other maternal serum markers for risk estimation of growth impairment in the first trimester.