30 FIRST TRIMESTER PREGNANCY-ASSOCIATED PLASMA PROTEIN A AND SUBSEQUENT ABNORMALITIES OF FETAL GROWTH

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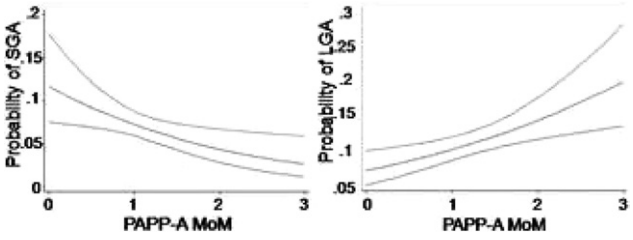
OBJECTIVE: To describe the relationship between first trimester pregnancy-associated plasma protein A (PAPP-A) and birth weight along its continuum and at its extremes.

STUDY DESIGN: We conducted a retrospective cohort study of 1,371 women who underwent first trimester screening for fetal aneuploidy and subsequently delivered at Magee-Womens Hospital. We linked first trimester PAPP-A with perinatal outcomes recorded in a longstanding electronic database. Extremes of fetal growth were defined as small for gestational age (SGA) <10% and large for gestational age (LGA) >90% or 4250 grams. Logistic regression modeling was used to assess the relationship between PAPP-A and birth weight.

RESULTS: In univariate analysis, first trimester PAPP-A correlates positively with birth weight along its continuum. As PAPP-A decreases, the risk of SGA increases; for every one multiple of the median (MoM) increase in PAPP-A, birth weight increases by 119 grams. PAPP-A <10%, <5%, and <1% were associated with an increasing adjusted odds ratio for SGA (2.0, 95% CI 1.2-3.5; 2.4, 95% CI 1.2-4.7; 9.3, 95% CI 3.4 -25.5, respectively). At the opposing extreme, PAPP-A >90% was associated with an adjusted odds ratio for birth weight >4250 grams of 2.3 (95% CI 1.2-4.5).

CONCLUSION: First trimester PAPP-A serves as a marker of placental function throughout pregnancy, correlating with birth weight along its continuum and at its extremes. Most clinically significant is the strong association between low PAPP-A and SGA, warranting further investigation of its utility as a screening tool.



Logistic regression of PAPP-A and probability of SGA and LGA

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31 ALTERED NR2B TRAFFICKING IN A DOWN SYNDROME MODEL MEDIATES LEARNING DEFICIT

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OBJECTIVE: Down Syndrome (DS, trisomy 21) is a major cause of mental retardation affecting 1/800 newborns. Using a Ts65Dn mouse model for DS and the Morris watermaze to assess learning, we have shown a learning deficit (Toso, 2007) in the adult Ts65Dn mouse as compared to wild type. NMDA receptors, specifically, the NR2B subunit is responsible for enhanced synaptic plasticity in paradigms of learning and memory. The expression of KIF17, a motor protein which transports NR2B subunits into the synaptic region, is shown to be parallel to increasing and decreasing expression of synaptic NR2B. While a down regulation of KIF17 is concomitant with an increase in the less plastic synaptic NR2A, subunit expression (Hirokawa, 2004). Our objective was to evaluate the expression of NR2B, NR2A and KIF17 in a mouse model for DS to correlate to mechanisms underlying learning deficits seen in Ts65Dn adult mice..

STUDY DESIGN: Using the well established Ts65Dn model for Down Syndrome(DS), adult brains (40-60 weeks old) were collected and Western blot anaylsis performed with antibodies for NR2A, NR2B and KIF17 and quantified using NIH Image software and actin standardization. Comparisons were made between DS (trisomic) and control (wild type) animals with ANOVA, $P<0.05$ was considered significant

RESULTS: Brains from 4 DS and 4control (wild type) from four litters were studied. Western blot revealed no significant difference in the levels of NR2A ($P=0.79$) and NR2B ($P=0.96$) in DS as compared to the wild type (control) animals. However there was a significant increase in KIF17 ($P=0.02$) expression in our control (wild type) as compared to the DS animals.

CONCLUSION: Although we found no significant changes in protein expression of total NR2A or NR2B subunits in the WT vs. Ts65Dn mice, there is a significant decrease in expression in KIF17 motor protein in the Ts65Dn animals. This may indicate a possible decrease in synaptic NR2B subunit as well as an increase in synaptic NR2A subunit which may underlie the learning deficit seen in the adult Ts65Dn mice

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32 MATERNAL AND FETAL FACTOR V AND METHLYENE TETRAHYDROFOLATE REDUCTASE (MTHFR) GENOTYPE AND FETAL/PLACENTAL THROMBOTIC AND INFLAMMATORY LESIONS

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OBJECTIVE: To explore the relation between maternal and fetal variation in Factor V and MTHFR genes and histologic evidence of fetal/placental inflammatory and thrombotic lesions

STUDY DESIGN: In this prospective observational cohort of 111 women with singleton gestations DNA was extracted from maternal and cord blood from all subjects. Factor V and MTHFR genotype assays on all mom-baby pairs were performed on an Illumina® platform. Single nucleotide polymorphism (SNP) selection was made using a linkage disequilibrium (LD) bin approach. LD bins are composed of SNPs that are very highly correlated with each other, where a single tag SNP can be used to predict the genotypes of other SNPs in the bin. Fifteen tagSNPs were selected in the MTHFR gene and 26 tagSNPs in the Factor V gene. All placentae were examined by a single blinded perinatal pathologist. The diagnoses of fetal/placental thrombosis and inflammation were made using the criteria of Redline et al.

RESULTS: After adjustment for multiple comparisons, one fetal SNP in MTHFR (rs17421462) and one fetal SNP in Factor V (rs10489185) demonstrated highly significant association with thrombotic and inflammatory lesions. In a multivariable model with adjustment for maternal race, smoking, and bacterial vaginosis, carriage of these polymorphic alleles was strongly associated with thrombotic and inflammatory lesions (fetal rs17421462: odds ratio 4.2, $p=0.02$. fetal rs10489185: odds ratio 0.18, $p=0.007$). There was no evidence of statistical interaction between these two SNPs.

CONCLUSION: Fetal genetic variation in MTHFR and Factor V is strongly associated with histologic evidence of fetal/placental inflammation and thrombosis. These genotypic effects are independent of each other and other environmental covariates.

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33 ASSESSMENT OF RISK FOR FETAL LOSS BY MATERNAL CHARACTERISTICS WITH FIRST AND SECOND TRIMESTER MATERNAL SERUM MARKERS

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OBJECTIVE: To develop and evaluate a method of estimating patient-specific risk for fetal loss by combining maternal characteristics with 1st and 2nd trimester serum markers.

STUDY DESIGN: Data was obtained on 35,603 women from the FASTER trial. Separate likelihood ratios (LRs) were estimated directly for significant maternal characteristics and, using a multivariate Gaussian model of the frequency distributions, for significant serum markers. Patient-specific risk was calculated by multiplying the incidence of fetal loss, as an odds, by the LRs for each maternal characteristic and for different serum marker combinations. Risks were aggregated to estimate the detection rate (DR) for a fixed 1%, 5% and 10% false-positive rate (FPR).

RESULTS: 193 women had fetal loss <20 weeks (early) and 189 >20 weeks (late). The significant characteristics were age, BMI, race, parity, threatened abortion and previous abortions; with a low DR when risk assessment was based on all of them. The significant markers for early loss were AFP, uE3 and PAPP-A; risk assessment based on all of them yielded 40-54% detection, and only increased slightly when characteristics and markers were combined (Table). Only inhibin was a significant marker for late loss and the DR was poor at 8%, 20% and 32% at FPRs of 1%, 5% and 10%, respectively, in combination with maternal characteristics.

CONCLUSION: Patient-specific risk assessment for early fetal loss using serum markers, with or without maternal characteristics, has a reasonably high detection.

	1% FPR	5% FPR	10% FPR
characteristics	4%	16%	24%
marker			
AFP	32%	44%	50%
uE3	27%	33%	36%
PAPP-A	8%	17%	24%
All	40%	49%	54%
characteristics + marker			
AFP	30%	46%	55%
uE3	28%	36%	43%
PAPP-A	4%	21%	54%
All	40%	50%	55%

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