PREMATURITY

Abstracts 9 – 17

Moderators: George Macones, MD; March of Dimes Representative, TBA

9 First-trimester prediction of preterm birth using ADAM12, PAPP-A, uterine artery Doppler and maternal characteristics

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OBJECTIVE: To estimate the efficiency of first-trimester A-disintegrin and metalloprotease 12 (ADAM12), pregnancy-associated plasma protein A (PAPP-A), uterine artery Doppler and maternal characteristics in the prediction of preterm birth.

STUDY DESIGN: This is a prospective cohort study of patients presenting for first-trimester aneuploidy screening between 11-14 weeks' gestation. Maternal serum ADAM12 and PAPP-A levels were measured by immunoassay, and mean uterine artery Doppler pulsatility indices (PI) were calculated. The primary outcome was preterm birth (PTB) <34 weeks' gestation. A secondary outcome of PTB <37 weeks' gestation was also evaluated. Logistic regression analysis was used to model the prediction of PTB using ADAM12 multiples of the median (MoM), PAPP-A MoM, and uterine artery Doppler PI MoM, either individually or in combination. Maternal characteristics identified as significant in a univariate analysis were also included in the models. Sensitivity, specificity, and area under the receiver-operating characteristic curves (AUC) were used to compare the screening efficiency of the models using non-parametric U-statistics.

RESULTS: Of 578 patients with complete outcome data, 36 (6.2%) delivered <34 weeks and 78 (13.5%) delivered <37 weeks. Median ADAM12 levels were significantly lower in patients who delivered <34 weeks (0.79 vs 1.10, P =.01) and <37 weeks (0.83 vs 1.02; p=.003) compared to those who did not. For a fixed false positive rate (FPR) of 20%, ADAM12, PAPP-A, and uterine artery Doppler identified 58%, 52%, and 62% of patients who delivered <34 weeks and 42%, 48%, and 50% of patients who delivered at <37 weeks, respectively. Combining these first-trimester parameters did not improve the predictive efficiency of the models. Excluding cases of indicated PTB for preeclampsia also did not significantly alter the predictive efficiency of the models.

CONCLUSION: While first-trimester ADAM12, PAPP-A, and uterine artery Doppler are each modestly predictive of PTB, combinations of these parameters do not further improve their screening efficiency.

Preterm Birth <34 Weeks			
Marker	AUC (95% CI)	Sensitivity	
		10% FPR	20% FPR
ADAM12	0.72 (0.59-0.84)	42%	58%
PAPP-A	0.77 (0.69-0.85)	38%	52%
Uterine Artery Doppler	0.74 (0.65-0.83)	38%	62%
ADAM12 + PAPP-A	0.77 (0.68-0.86)	42%	58%
ADAM12 + Uterine Artery Doppler	0.76 (0.66-0.86)	42%	62%
ADAM12 + PAPP-A + Uterine Artery Doppler	0.78 (0.69-0.87)	42%	65%

10 Fetuin-mediated aggregation of amniotic fluid proteins into calcifying nanoparticles (CNP) and preterm premature rupture of membranes (PPROM)

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OBJECTIVE: Disturbances in mineral-protein composition of biological fluids result in fetuin-mediated nucleation of hydroxyapatite (insoluble CaP), depletion of essential proteins and formation of CNPs. This process is analogous to the formation of prions and amyloid and results in deposition of mature CNPs in surrounding tissues and cytotoxicity. Here, we explored potential mechanisms through which amniotic fluid (AF) CNP formation may lead to PPROM.

STUDY DESIGN: The kinetics of CNP formation in AF was studied in a long-term culture method of cell-free sterile-filtered amniocentesis samples from 10 preterm women (GA: 27±2 weeks). Known CNP constituents [fetuin, ionized Ca, and inorganic phosphate (Pi)] were assessed in immature (soluble) and mature (insoluble) CNP aggregates. IL-6 was explored by ELISA as an endogenous AF protein trapped during the process of CNP formation. Biological activity of immature and mature CNPs was evaluated in an amniochorion explant system by conventional histological criteria of necrosis. CNP protein co-aggregation was imaged by immuno-electron microscopy. Glucose metabolism was studied via a kinetic assay. For proof of concept, we examined in-vivo the levels of soluble fetuin and IL-6 in AF of 50 women with (n=27) and without (n=23) PPROM. All delivered preterm in the absence of infection.

RESULTS: 1) Compared to uncultured AF, soluble fetuin, Ca, Pi and IL-6 levels were significantly decreased by CNP formation (all P<.05); 2) Double immuno-gold staining of AF CNPs demonstrated co-aggregation of fetuin and IL-6 in a non-random lattice; 3) Fetal membranes exposed to immature CNPs display a significantly faster rate of glucose metabolism (P<.001) and necrosis; 4) AF of women with PPROM showed significantly lower IL-6 (P<.03) and fetuin (P<.01) levels compared to intact membranes group, with a significant direct correlation between fetuin and IL-6 (R=.413, P=.003).

CONCLUSION: This study supports the premise that CNP formation alters the protein composition of AF and disrupts the function of fetal membranes leading to PPROM and preterm birth.