PREMATURITY

Abstracts 9 – 17

Moderators: Brian Mercer, MD; Alan Fleischman, MD, Medical Director, March of Dimes

9 Calcifying nanoparticles (NP) as novel etiologic agents of idiopathic preterm birth (iPTB) and preterm premature rupture of the membranes (PPROM)

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OBJECTIVE: NP (formerly nanobacteria) are self-replicating calcium-protein complexes that aggregate into 3D structures similar to prions and amyloids. Their involvement in degenerative diseases (i.e. atherosclerosis) has been proposed. NP are smaller than the accepted size for bacteria (200 nm) and do not match current criteria for living organisms. NP disrupt key signaling pathways and lead to cell dysfunction and death. We explored the involvement of NP in pathogenesis of PTB.

STUDY DESIGN: Amniochorion and placental tissues from 61 PTB women (GA: 28 [24-32] wks) were investigated. Tissue micro-calcifications were quantified by vonKossa and Alizarin S staining. Immunostaining for á2-Heremans Schmid glycoprotein (AHSG, endogenous inhibitor of biomineralization and known component of NP) was performed. NP formation involves consumption of soluble AHSG (sAHSG) which was evaluated by ELISA in amniotic fluid (AF) of 104 PTB women (GA: 29 [18-34] wks) and 22 women (GA: 30 [21-35] wks) without intra-amniotic inflammation (IAI) who delivered at term. To explore NP formation *in vitro* we used a long-term culture system of sterile-filtered AF and electron microscopy (EM). Functional effects of AF-derived NP were tested in an amniochorion explant system for IL6 (inflammation) and LDH (necrosis) release.

RESULTS: **1)** 3 micro-calcification patterns were discovered: plaques, granules (in placenta villi) and finely dispersed particles (in membranes and villi); **2)** AHSG staining was found in all 3 patterns; **3)** AHSG deposits were less prevalent in PPROM vs. PTB intact membrane cases ($P<0.05$) independent of IAI and histological chorioamnionitis; **4)** PPROM women had lowest AF sAHSG levels ($P<0.001$), independent of IAI and GA; **5)** *In vitro*, AF-derived NP were visualized after 4 wks of incubation with sAHSG consumption in supernatant; **6)** NP were round 20-200 nm aggregates at EM; **7)** Amniochorion exposed to AF-derived NP showed evidence of cell death but not inflammation.

CONCLUSIONS: This study provides evidence that human AF harbors NP formation and propagation and points toward their role in pathogenesis of iPTB and PPROM.

10 The frequency and clinical significance of intra-amniotic inflammation in women with preterm labor symptoms without cervical change

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OBJECTIVE: Preterm labor has been traditionally defined as regular uterine contractions with progressive cervical change, and there have been strong evidences on the relationship between intra-amniotic infection and/or inflammation and adverse pregnancy outcomes in preterm labor. However there is a paucity of information regarding the clinical significance of intra-amniotic infection and/or inflammation in patients with regular uterine contractions without cervical change. The objective of this study was to determine the frequency and clinical significance of IAI in patients with regular uterine contractions and intact membranes without cervical change in preterm gestations.

STUDY DESIGN: Amniocentesis was performed in 127 patients with regular uterine contractions and intact membranes with cervical dilatation of ≤1 cm but without cervical change. Amniotic fluid (AF) was cultured for aerobic and anaerobic bacteria and genital mycoplasmas and assayed for matrix metalloproteinase-8 (MMP-8). Intra-amniotic inflammation was defined as an elevated AF MMP-8 concentration (>23 ng/mL). Nonparametric tests and survival methods were used for statistical analysis.

RESULTS: The frequency of intra-amniotic inflammation (IAI) was 11.8% (15/127) in patients with regular uterine contractions without cervical change. Patients with IAI had higher rate of delivery within 7 days after amniocentesis (64.3% vs. 13.9%, $P<0.001$) and preterm delivery before 37 weeks of gestation (92.9% vs. 35.2%, $P<0.001$) than those without IAI. Patients with IAI had significantly shorter amniocentesis-to-delivery interval than those without IAI by survival analysis ($P=0.017$) and this difference remained significant after adjustment for gestational age at amniocentesis.

CONCLUSIONS: Intra-amniotic inflammation is present in approximately 12% of patients with regular uterine contractions without cervical change and is a significant risk factor for impending preterm delivery.

11 17-hydroxyprogesterone for twin pregnancy: no reduction in prematurity or neonatal morbidity

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OBJECTIVE: To determine whether prophylactic 17-alpha-hydroxyxprogesterone caproate (17P) given to mothers with twin pregnancy will reduce composite neonatal morbidity by decreasing the rate of preterm delivery.

STUDY DESIGN: Placebo-controlled, double-blind, multicenter, randomized clinical trial. Mothers with diamniotic-dichorionic twins were randomized to 17P (250 mg IM) or placebo (castor oil vehicle, 1 mL), starting at 16-23 wks' gestational age (GA), repeated weekly until 34 wks' GA. Sample size 240 mothers (480 babies) was calculated to give 80% power to detect reduction of composite neonatal morbidity from 45% with placebo to 30% with 17P.

RESULTS: 160 mothers were randomized to 17P, 80 to placebo at mean GA 20 wks. Baseline characteristics were similar between the groups. There was no significant difference in composite neonatal morbidity (14% with 17P vs 12% with placebo), or in mean GA at delivery (35.3 wks vs 35.9 wks), delivery <28 wks (2% vs 1%), <32 wks (9% vs 5%), <35 wks (33% vs 26%). There were no perinatal deaths in the 17P group and 3 neonatal deaths in the placebo group, two after withdrawal of life support because of fetal anomalies not discovered prenatally and one attributed to neonatal sepsis.

CONCLUSIONS: Prophylactic administration of 17P did not reduce the rate of preterm delivery or neonatal morbidity. Contrary to our previous report that 17P was associated with an increased risk of midtrimester loss in triplet pregnancies, we found no such association in this trial of twin pregnancies.