39 SERIAL MATERNAL SERUM INTERLEUKIN-6 LEVELS IN PRETERM PREMATURE RUPTURE OF MEMBRANES PATIENTS PREDICTS IMPENDING FUNISITIS

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OBJECTIVE: Preterm premature rupture of membrane (PPROM) patients are managed expectantly until labor or infection is present. We previously reported that maternal serum (MS) interleukin (IL)-6 is elevated at delivery in PPROM with infection. Our objective was to determine if MS IL-6 is elevated before clinical infection or labor in PPROM patients with subsequent funisitis.

STUDY DESIGN: All PPROM patients were eligible for this cohort study. After IRB approval, 76 subjects with PPROM consented to daily blood sampling. Aliquots of sera were frozen at -80C and IL-6 levels determined by ELISA (CC Lab, MD). MS IL-6 levels within 12-36 hours of delivery (without clinical infection or labor) were compared to the first sample (>48 hrs) prior to delivery in subjects with and without funisitis. A power analysis calculated that 35 subjects were required to detect a doubling in MS IL-6. Data were analyzed by Mann Whitney U (StatView, Cary, NC).

RESULTS: Of the 76 PPROM subjects enrolled, 36 remained undelivered >48 hours without clinical infection or labor, had daily samples and pathology. Subjects were divided into those with (n = 13) and without funisitis (n = 23). There was no difference in age, race, insurance or prior preterm birth between groups. Median MS IL-6 levels were significantly higher at 12-36 hours prior to delivery in those with funisitis compared to those without (7.9 vs 1.5 pg/mL, P = .001). The change in MS IL-6 levels between 12-36 hour and >48 hour samples was calculated for each subject and compared. Subjects with funisitis had a significant rise in MS IL-6 compared to those without funisitis (5.2 vs 1.1 pg/mL, P = .01).

CONCLUSION: MS IL-6 levels are higher 12-36 hours prior to delivery in PPROM patients with subsequent funisitis. MS IL-6 may identify those PPROM patients at risk for both intrauterine and fetal infection. Identifying PPROM patients at increased risk for maternal/fetal infection will improve our ability to manage these patients.

40 PRETERM PREMATURE RUPTURE OF MEMBRANE (PPROM): VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) AND ITS ASSOCIATION WITH THE DURATION OF RUPTURE TO DELIVERY AND INFECTION

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OBJECTIVE: We hypothesize that local activity of VEGF in fetal membranes activates tissue plasminogen activator and matrix metalloproteinases resulting in collagen breakdown of the amnion and leading to membrane rupture. We seek to determine whether the time duration between PPROM and delivery is reflected in the expression of VEGF and Flt-1 genes in the decidua, amnion and chorion and whether this upregulation can be present in the absence of infection.

STUDY DESIGN: Membranes were sampled from a region distinct as the rupture site from preterm patients delivering either 1) Vaginally or by cesarean section with premature rupture of membranes prior to onset of labor (group 1) or 2) C/S with intact membranes in labor (group 2). Control subjects included those with intact membranes, not in labor, and delivered by C/S. The duration of rupture to delivery ranged from 4 hours-12 days. Expression of genes was analyzed by in situ hybridization. IL-6 gene expression in fetal membranes were analyzed using Northern Blot Analysis.

RESULTS: VEGF and Flt-1 gene expressions were increased in the amnion and decidua of patients in study group 1 with PPROM > 4 hours (P < .00001) with a proportional increase in the expression of these genes from 4 hours-12 days of rupture (P < .005). There was an upregulation of IL-6 gene expression in the fetal membranes with the duration of rupture between 12 hours-8 days vs 4-6 hours. VEGF gene expression was upregulated in decidua samples with minimal IL-6 gene expression suggesting an increased expression of the VEGF gene without evidence of infection.

CONCLUSION: Increasing levels of VEGF and Flt-1 mRNA correlate with an increasing latency period between PPROM and delivery. The expression of these genes do not appear to be labor related. In the absence of infection, VEGF may be the primary mediator leading to PPROM. (Supported by CROWN.)

41 COMBINED ANTIBIOTIC/INTERLEUKIN-10 THERAPY INCREASES INTERVAL TO DELIVERY IN A RAT MODEL OF INFECTION-MEDIATED PRETERM BIRTH

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OBJECTIVE: This study was designed to test the efficacy of combined antibiotic/IL-10 therapy in a rat model of infection-mediated preterm birth.

STUDY DESIGN: Timed-pregnant Sprague-Dawley rats (N = 15) had intrauterine catheters placed on day 15 of a 22-day gestation. Day 17, animals were randomly assigned 1 of 3 groups: 1) saline controls, 2) *Escherichia coli* (*E. coli*) (1×103 colony forming units), or 3) *E. coli* + antibiotic (Abx) (Rocephin, 20mg/Kg IM BID) + IL-10 (200ng/day). Animals in groups 2 and 3 received inoculation of *E. coli* on day 17 while group one received saline only. On days 18-21, group 3 received a daily infusion of IL-10 (200ng) along with BID Abx. Animals were observed and the interval to delivery, live birth weights, and day 2 weights were recorded.

RESULTS: The live birth rates for groups 1, 2, and 3 were 68%, 0%, and 42% respectively. Group 1 delivered, term, 120.5 ± 3.9 hrs (mean ± SD) post treatment. Infusion of *E. coli* (2) resulted in all pups being preterm (81 ± 12.7 hrs) but stillborn. Animals in group 3 experienced term, prolonged (134 ± 16.6 hrs) deliveries. Live birthweights of groups 1 and 3 were not different (P = .100). ANOVA was used to compare interval to delivery. There were no differences between groups 1 and 3 (P = .147). However, there were significant differences between groups 1 and 2 (P = .001) as well as groups 2 and 3 (P < .001).

CONCLUSION: This treatment protocol dramatically reduced fetal wastage associated with intrauterine infection providing evidence supporting the potential efficacy of antibiotic/cytokine therapies for the treatment of infection-mediated preterm birth.

Table

	SALINE	*E. COLI*	*E. COLI*/ ABX/IL-10	*P*
Interval to del (hrs)	120.5 ± 3.9	81 ± 12.7	134 ± 16.6	<.001
Live birth weight (gm)	5.76 ± .628	-	5.49 ± .632	.100
Day 2 weight (gm)	6.31 ± .768	-	6.15 ± .939	.553

42 EFFECTS OF PHENOBARBITAL AND MULTIPLE-DOSE ANTENATAL/POSTNATAL STEROID ON DEVELOPMENTAL OUTCOME AT AGE 7 YEARS

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OBJECTIVE: To determine the effects of phenobarbital and repeated antenatal/postnatal steroid use on the Wechsler Intelligence Scale for Children (WISC-III) IQ scores and the Wide Range Achievement Test (WRAT3) achievement scores at age 7 years.

STUDY DESIGN: A secondary analysis of a double-blinded clinical trial (phenobarbital-vitamin K versus placebo); WISC-III and WRAT3 testing was performed on 7-year old children whose mothers participated in a trial to determine if antenatal phenobarbital-vitamin K prevented intracranial hemorrhage (ICH). Antenatal steroid therapy was repeated weekly from study entry until delivery, discharge or 34 weeks gestation.

RESULTS: 291 of 372 newborns (78%) whose mothers participated in the trial were followed up at age 7 years. Comparing mean (± SD) WISC-III scores in the placebo versus treatment groups, there were no differences (P > .4) in Full Scale IQ (100.3 ± 14.2 vs 100.6 ± 14.2), Performance IQ (100.3 ± 14.6 vs 101.5 ± 15.6) and Verbal IQ (100.2 ± 14.9 vs 99.6 ± 13.7). Comparing mean (± SD) WRAT3 standardized scores in the placebo versus treatment groups, there were no differences (P > 0.4) in Reading (97.3 ± 13.9 vs 98.0 ± 14.9), Spelling (95.8 ± 12.7 vs 95.3 ± 13.3) or Arithmetic (95.9 ± 13.8 vs 94.5 ± 14.5). Whether using a cut-off of 1, 1.5, or 2 standard deviations below the mean, there were no differences in proportion of lower scores between the placebo and treatment groups in any of the above WISC-III or WRAT3 scores. Duration of antenatal steroid or phenobarbital therapy did not affect WISC-III or WRAT3 scores analyzed by multivariate analysis (P value > .10) controlling for numerous potentially confounding variables including obstetrical complications, gestational age at birth, occurrence of severe ICH, postnatal steroid, and maternal education.

CONCLUSION: Exposure to antenatal phenobarbital or to multiple courses of antenatal/postnatal steroid did not affect intelligence or achievement scores at age 7 years.