CONCLUSION: In PTL-I, the CVF proteome is measurably altered by IAI. A prototype multiple-marker test based on the concentrations of 5 distinct proteins in CVF appears to discriminate between IAI and non-infected cases, potentially reducing need for amniocentesis. Such a test could be very useful in the management of PTL-I. Research regarding the role of various proteins in CVF may yield insight into the pathophysiology of PTL.

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14 Identification of fetal and maternal single nucleotide polymorphisms in candidate genes that predispose to spontaneous preterm labor with intact membranes

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OBJECTIVE: Preterm labor/delivery can be caused by the activation of several pathologic pathways. A genetic association study was undertaken to determine whether the maternal and/or fetal carriage of single nucleotide polymorphisms (SNPs) in candidate genes predisposes to spontaneous preterm labor/delivery.

STUDY DESIGN: A case-control study was conducted. Cases were patients with preterm labor who delivered <37 weeks. Controls consisted of women who delivered a normal AGA neonate at term; 190 candidate genes and 775 SNPs were studied. Cases were 223 mothers and 179 fetuses while controls consisted of 599 mothers and 628 fetuses. SNP discovery was performed by DNA sequencing, and genotyping was carried out using the MassARRAY(TM) System. Single locus and haplotype association analyses were performed separately on maternal and fetal DNA variants. Single locus tests of association were performed using logistic regression (additive model). We used a linkage disequilibrium based SNP pruning approach in the Plink software with a maximum r^2 and a false discovery rate to correct for multiple testing ($q^*=0.15$).

RESULTS: 1) The strongest fetal single locus association with spontaneous preterm birth was observed in the interleukin 6 receptor (*IL6R*) (OR=2.07 95% CI [1.42-3.02], p=0.000148); 2) The strongest maternal single locus association with spontaneous preterm labor/delivery was observed in a SNP in tissue inhibitor of metalloproteinase 2 (*TIMP2*) (OR=1.98 95% CI [1.38-2.83], p=0.000197); 3) These associations remain statistically significant after correction for multiple comparisons; 4) Global haplotype analysis indicated an association between a fetal DNA variant in insulin-like growth factor 2 (global p=0.004) and maternal alpha 3 type IV collagen isoform 1 (*COL4A3*, global p=0.007).

CONCLUSION: 1) A SNP involved in the control of fetal inflammation (*IL6R*) doubled the risk of preterm birth; and 2) DNA variants in maternal genes encoding for proteins involved in extracellular matrix biology also increased the risk of preterm birth.

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15 17P vehicle, castor oil, exerts a uterotonic effect in human myometrium in pregnancy

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OBJECTIVE: There is evidence that the clinical use of 17 Hydroxyprogesterone caproate (17P) in women at high risk of preterm delivery (PTD), results in a reduction in the rate of PTD, and a reduced risk of serious neonatal morbidity. The mechanism by which 17P exerts this effect is unknown. The possibility that the vehicle for 17HP, castor oil, exerts an independent effect on human uterine contractility, has previously been questioned, and is hitherto unknown. The aim of this study was to evaluate the potential effects on contractility of exposure of isolated human myometrial preparations, obtained during pregnancy, to castor oil.

STUDY DESIGN: Biopsies of human myometrium were obtained at elective cesarean section (n=8). Dissected myometrial strips suspended under isometric conditions, had contractility induced, for a 30 minute period using oxytocin (0.5nM). Strips were removed from the tissue bath and inserted in Castor Oil or physiological salt solution (PSS), for a 30 minute period. Strips were then re-suspended under isometric conditions and exposed to further oxytocin challenge. Contractile integrals were expressed in relation to the first challenge, and compared between study and control groups.

RESULTS: Strips exposed to castor oil demonstrated increased contractile activity elicited by oxytocin after the castor oil exposure (165.53%± 17.03%, n=8, P=0.004), in comparison to that measured prior to its exposure. For strips exposed to PSS only, the second oxytocin challenge reduced contractile activity (72.57%±7.48%, n=8, P=0.003). Comparison of the contractile activity, between castor oil and PSS exposed strips, revealed a significant increase in contractile activity for those exposed to castor oil (p<0.001).

CONCLUSION: These findings indicate that exposure of human myometrial preparations to castor oil results in an enhanced state of contractility in this in vitro model, in comparison to control experiments. The use of castor oil as placebo for 17P studies may be linked to increased contractility, and higher preterm delivery rates, among the placebo arm.

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16 Does mid-trimester cervical length 25 mm predict preterm birth in high risk women?

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OBJECTIVE: To estimate whether mid-trimester cervical length (CL) ≥ 25 mm in high-risk women is predictive of preterm birth.

STUDY DESIGN: Planned secondary analysis of the NICHD-sponsored cerclage trial. Women with documented prior spontaneous preterm birth (SPTB) at 17-$33^{6/7}$ weeks' gestational age (GA) underwent serial cervical ultrasound scans initiated between 16 and $21^{6/7}$ weeks. Fundal pressure-induced and spontaneous dynamic shortening were assessed to determine the shortest CL. The final scan was scheduled before 23 weeks. Women whose CL was < 25 mm were invited to consent for the intervention trial.

RESULTS: Of 1014 eligible women who began ultrasound screening, 318 had CL < 25 mm. Delivery dates were unavailable in an additional 24 (3.4%), leaving a study population of 672 for this analysis. The median (interdecile range) GA at the qualifying scan was 21.7 (19.1, 22.7) weeks, with a median CL of 34 (27, 42) mm. For comparison, the incidence of preterm birth < 35 wks was 42% in the 153 women who had CL < 25 mm and were randomized to no cerclage, as compared to 16% in this study population of women whose CL was ≥ 25 mm (p<0.0001). In a linear regression model, CL did not predict birth GA (p=0.15). Only in a Cox survival model was there a significant rela-

tionship between CL and time to birth (p=0.03), but this effect was null after controlling for maternal age. In logistic regression models, CL did not significantly predict PTB < 24, < 28, < 35, or < 37 weeks. Stratifying CL by 25-29 mm versus 30 mm or greater also had no significant predictive value for these 4 preterm birth cutoffs.

CONCLUSION: Women at high risk for recurrent preterm birth, but whose cervical length at < 23 weeks′ gestation remains ≥ 25 mm are still at increased risk of recurrent PTB (16% delivered < 35 weeks); however, CL measured before 23 weeks, whether considered on a continuum or stratified to consider CL′s near the 25 mm cutoff (25-29 mm), does not predict PTB.

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17 Epithelial protection and repair: the role of trefoil factor 1 in the mouse cervix through pregnancy

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OBJECTIVE: The cervix remodels throughout pregnancy in preparation for parturition and includes stages of softening, ripening and dilation. Understanding the molecular processes that regulate each phase is critical for identification of preterm birth risk factors due to cervical malfunction. Trefoil factor 1 (Tff1) is a member of a family of secreted proteins that play an important role in the protection and restitution of the gastrointestinal mucosal epithelium. We previously determined a temporal and robust mRNA expression of Tff1 in the pregnant cervix with maximal expression prior to birth and rapid decline postpartum. Mice deficient in Tff1 will be used to understand the role Tff1 may play in barrier protection and repair of cervical epithelia during pregnancy.

STUDY DESIGN: Cervical Tff1 protein abundance and cell localization was evaluated by western blotting and immunohistochemistry. The role of Tff1 in epithelial cell function during cervical remodeling was assessed by morphological assessment of Tff1−/− cervices and evaluation of genes normally expressed in the epithelia during cervical ripening.

RESULTS: Protein expression of Tff1 mirrors mRNA expression and is confined to differentiated squamous epithelia. Morphology of the Tff1−/− cervix appears normal before and during cervical ripening. Gene expression of hyaluronan synthase 2, keratin 16, and serine protease inhibitor kazal type 5 were suppressed on gestation d15 and d18 compared to wild type controls but recovered postpartum. Claudin 2 had elevated expression in Tff1−/− mice on day 18 compared to wild types, but claudin 1 had normal expression.

CONCLUSION: These studies confirm the expression of Tff1 in the cervical squamous epithelia and suggest that some but not all aspects of barrier regulation are compromised in the absence of Tff1. The altered barrier properties of the cervical epithelia in Tff1 null mice suggest that these mice may be a useful model to evaluate susceptibility to infection mediated preterm birth upon epithelial insult when there is a reduced capability to repair cervical epithelia.

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