98 EPITHELIAL CELL DIFFERENTIATION PATHWAY: A PLAYER IN POSTPARTUM CERVICAL REPAIR NOT RIPENING JUAN GONZALEZ[1], HUA XU[1], ELLA OFORI[2], MICHAL ELOVITZ[1], [1]University of Pennsylvania, OBGYN; Maternal and Child Health Research Program, Philadelphia, Pennsylvania, [2]University of Pennsylvania, OBGYN; Maternal and Child Health Research Program, Pennsylvania

OBJECTIVE: Prior work from our lab demonstrated novel pathways between preterm (PT) and term (T) cervical ripening using microarray. One pathway–epithelial cell differentiation was significantly regulated in T but not PT cervical ripening. We sought to determine if this pathway was indeed specific for term cervical ripening and could serve to differentiate molecular mechanisms of PT and T parturition.

STUDY DESIGN: 3 sets of experiments were performed using CD-1 mice. (1) Gestational time course: non-pregnant, E15, E17, E18.5, postpartum day 1 and 2. (n=3-6/group) (2) On E15, dams were randomized to a) no intervention b) Intrauterine infusion of LPS (n=6/group) (3) On E15, a non-infectious model of PTB with RU486 or control (n=5/group). For #1, cervical tissues were harvested in am of gestational day. For 2#2 and #3), cervices were harvested 6 hrs after treatment. QPCR and IHC were performed.

RESULTS: Keratin 8, keratin 16, desmoglein1 alpha, desmoglein1 beta mRNA expression was significantly different over the gestational time course ($P<0.001$ for all targets). IHC confirmed an increase in desmoglein 1 expression at term.

CONCLUSION: Activation of the epithelial cell differentiation pathway does not appear necessary for inflammation-induced preterm cervical ripening. The up-regulation of this pathway at T and during postpartum suggests involvement in the process of cervical remodeling. Importantly, in PT inflammation, an up-regulation of these pathways does not occur. These findings suggest a lack of appropriate cervical remodeling may be a risk factor for future PT birth.

QPCR Confirmation of Genes Involved in Cervical Remodeling (fold difference in mRNA expression)

	Preterm (LPS)	Preterm (Ru486)	Term	Postpartum Day 1/E 15
	E 15 LPS/ E 15	E 15 Ru486/ E 15	E 18.5/ E 15	PPD 1/E 15
Keratin 8	−1.07	8.31*	3.77	2.31
Keratin 16	38.85	68.25	329.09*	325.94*
Desmoglein 1 alpha	−2.82	3.1	36.83*	24.79
Desmoglein 1 beta	−4.64	3.15	19.18	19.59

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99 SFLT1 POLYMORPHISMS AND RISK OF PREECLAMPSIA (PE) MELISSA L. WILSON[1], DANIEL H. DESMOND[2], T. MURPHY GOODWIN[3], SUE A. INGLES[4], [1]University of Southern California Keck School of Medicine, Obstetrics and Gynecology & Preventive Medicine, Los Angeles, California, [2]University of Southern California Keck School of Medicine, Obstetrics and Gyecology, Los Angeles, California, [3]University of Southern California Keck School of Medicine, Obstetrics and Gynecology, Los Angeles, CA, [4]University of Southern California, Preventive Medicine, Los Angeles, California

OBJECTIVE: Numerous studies have reported elevated sFLT1 levels and expression in preeclamptic pregnancies. However, there have been no published reports to date examining the role of polymorphism in the sFLT1 gene in predisposing to PE.

STUDY DESIGN: Cases of PE and controls were recruited retrospectively from delivery logs and during postpartum hospital stays from 1999-2008. Controls were matched to cases on the basis of maternal and gestational age. DNA was collected from both the mothers and their infants and a risk factor questionnaire was completed. Four SNPs genotyped using TaqMan assays. Statistical analysis was conducted using Stata 9.2. For all SNPs, homozygotes for the rare allele were collapsed with heterozygotes to increase statistical power. Logistic regression was used to model the association between genotypes and PE risk, adjusting for maternal age and gestational age at delivery.

RESULTS: Genotype frequencies among controls did not depart from Hardy-Weinberg equilibrium and the rate of genotyping failure was below 2% in all of the polymorphisms studied. Offspring carrying either one or two copies of the A allele (rs664393) were at decreased risk of being born to a preeclamptic mother compared to those with no A alleles (OR = 0.5, 0.3-1.0). None of the maternal sFLT1 genotypes were statistically significantly associated with the risk of PE although there is a suggestion that mothers carrying at least one G allele (rs3751395) or at least one A allele (rs7983774) are at increased risk of PE(OR=1.4, 0.9-2.3; OR=1.4, 0.8-2.4, respectively).

CONCLUSION: Based on our understanding of the biological interrelationships between sFLT1 and its ligands, VEGF and PGF, we expect biological and statistical interactions between polymorphisms in these genes, potentially explaining the lack of statistically significant main effects for most of the sFLT1 polymorphisms studied.

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100 EXPOSURE TO PRENATAL INFLAMMATION RESULTS IN HYPERMETHYLATION AND ALTERATION OF GENE PATHWAYS INVOLVED IN NEUROBEHAVIORAL DISORDERS MICHAL ELOVITZ[1], JINGHUA CHAI[2], ELLA OFORI[3], JUAN GONZALEZ[2], [1]University of Pennsylvania, OBGYN; Maternal-Child Health Research Program, Philadelphia, Pennsylvania, [2]University of Pennsylvania, Philadelphia, Pennsylvania, [3]University of Pennsylvania, Pennsylvania

OBJECTIVE: Prenatal inflammation represents a significant risk factor for adverse neurodevelopment. Intrauterine inflammation occurs in approximately 20% of all pregnancies with a much higher prevalence in preterm births. The objective of this study was to determine if in utero exposure to inflammation results in genetic and epigenetic modifications in the prepubescent mouse brain.

STUDY DESIGN: CD-1 timed-pregnant mice on E18. 5 were randomized to intrauterine infusion with saline or LPS (n=18 per group). Number of live pups and maternal morbidity was recorded. On PND 2, litters were culled. On PND 21, brains from pups were harvested and processed for QPCR, IHC or epigenetic studies. QPCR was performed to assess expression of genes involved in an immune response, glial differentiation, neurogenesis, and neurotransmission. IHC was performed for H&E and markers of glial development.

RESULTS: Intrauterine inflammation on E18 resulted in 20% maternal mortality and a live pup rate of 65%. LPS-exposed dams had smaller litter sizes (P=.02) compared to controls. On PND 7, neonatal weights were not significantly different. On PND 21, cytokine mRNA expression was not different in LPS vs. saline exposed pups. However, several genes in the studied gene pathways were differentially regulated in LPS-exposed pups: dopamine beta hydroxlase (P=0.013), GFAP (P=0.04), MAG (0.04), MBP (0.04), PLP (<0.001), auts2 (0.03) and MeCP2 (0.005). H&E did not demonstrated structural abnormalities. GFAP staining was increased in periventricular regions. Global hypermethylation was present in both male and female pups exposed to LPS in utero ($P<0.0001$).

CONCLUSION: Exposure to intrauterine inflammation results in significant alterations in gene expression and epigenetic modifications in the prepubescent mouse brain, in the absence of overt structural injury. These abnormalities are not secondary to a persistent immune response. Epigenetic modifications from prenatal inflammation may be a critical mechanisms for the observed increased in cognitive and neurobehavioral outcomes in ex-preterm infants.

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101 DO OTHER ELEMENTS OF THE OBSTETRICAL HISTORY PROVIDE A POSSIBLE INDICATION FOR PROGESTERONE SUPPLEMENTATION? SECONDARY ANALYSIS FROM THE PROGESTERONE VAGINAL GEL TRIAL JOHN O'BRIEN[1], EMILY DEFRANCO[2], DAVID HALL[3], JAMES PHILLIPS[4], GEORGE CREASY[5], [1]Central Baptist Hospital, Perinatal Diagnostic Center, Lexington, Kentucky, [2]University of Cincinnati, Cincinnati, Ohio, [3]Stellenbosch University, Tygerberg Hospital, Tygerberg, South Africa, [4]Sage Statistical Solutions, Inc., Efland, North Carolina, [5]Columbia Laboratories, Inc, Livingston, New Jersey

OBJECTIVE: Because obstetrical history can identify populations at varied risk for preterm birth, we desired to assess the utility of progesterone therapy for the prevention of recurrent preterm birth in subgroups whose risk profile varied based on element in their history.

STUDY DESIGN: A secondary analysis was performed of women enrolled into a preterm prevention trial utilizing Procheive® 8% (90 mg) intravaginal, daily progesterone gel or placebo. Fisher's exact test and Cochran-Mantel-Haenszel (CMH) test were utilized to compare outcomes in defined subgroups based on number of prior preterm birth and gestational age at preterm birth.

RESULTS: 668 women were enrolled in the trial with data available for analysis in 620 participants. Demographic characteristics were similar between the groups. The rate of preterm birth ≤32 weeks is shown in the Table. No single subgroup, based on obstetric historical factors, benefitted more than the others, P = 0.49 by CMH for each analysis.

CONCLUSION: Utilizing a particular element of obstetrical history to define an indication for progesterone supplementation is not supported by these data.

Response to Progesterone Therapy Based on Elements of Obstetrical History

Number of PTBs	Treated, n (%)	Placebo, n (%)	P value
Single (n=462)	20 of 236 (8.5)	21 of 226 (9.3)	.870
Multiple (n=152)	10 of 73 (13.7)	15 of 79 (19.0)	.512
Timing of Prior PTBs			
<28 weeks (n=160)	14 of 81 (17.3)	13 of 79 (16.5)	1.0
28+0 to 31+6 (n=168)	10 of 80 (12.5)	11 of 88 (12.5)	1.0
≥32 weeks (n=262)	5 of 138 (3.6)	10 of 124 (8.1)	.182

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