117.7 mcg/l, IQR 72.4-231.8) were separately compared to controls (P = .04 and P<.001, respectively). Crude OR for PTD in the highest TAT quartile relative to the lowest one was 2.56 (95% CI, 1.40-4.86; P = .003). This point estimate was only minimally reduced in multivariable analysis controlling for history of PTD and gestational age at collection (adjusted OR 2.29, 95% CI 1.17-4.62; P =.01). Despite these distinct differences, the area under the ROC curve was only .62 (95% CI, .56-.69), indicating poor performance of TAT concentration as a risk discriminator.

CONCLUSION: Amniotic fluid level of TAT complexes in the second trimester is elevated in women who subsequently deliver preterm, suggesting that thrombin generation may be involved in the various etiopathogenic mechanisms leading to PTD. However, second trimester amniotic fluid TAT level is not a useful independent predictor of PTD.

11 The accuracy of fetal fibronectin and cervical length in women with signs of preterm labor before 34 weeks: a nationwide cohort study in The Netherlands (APOSTEL1 study)

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OBJECTIVE: We estimated the accuracy of cervical length (CL) and fetal fibronectin (fFN) measurement in predicting preterm delivery within 7 days among women with signs of preterm labor.

STUDY DESIGN: We performed a nationwide cohort study in all 10 perinatal centers in the Netherlands between December 2009 and May 2012. We obtained fFN status and CL in women with threatened labor between 24 and 34 weeks gestational age with intact membranes. The study group consisted of women admitted directly to tertiary hospitals and women referred from secondary centers. Aim of the risk assessment was to correctly identify women who will not deliver, without too many unnecessary referrals. We estimated accuracy of fFN and CL separately, and then compared strategies that combine fFN and CL measurements in different ways, in which we varied CL cut-off values. The accuracy of different strategies and cut-offs was assessed using receiver operating curve analysis.

RESULTS: We report on 559 of the 660 included women (85%). Full data will be presented at the congress. In total 87 (16%) women delivered within 7 days after inclusion. fFN only had a sensitivity of 76% (95%CI: 66-83%) and a specificity of 58% (95%CI: 54-62%). At the same sensitivity level as fFN, CL had a higher specificity of 80% (95%CI: 76-84%, p<0.001). Combining fFN with CL improved overall accuracy compared to single testing. CL measurement, and subsequent fFN testing in case of a CL between 15 mm and 30 mm had the same high negative predictive value as several other strategies (98%; 95%CI: 96-99%), at the highest specificity 67% (95%CI: 62-71%). The positive predictive value was 34% (95%CI: 28-40%), thus reducing unnecessary referrals from 209 of 472 with CL only to 157 of 472 (p<0.001).

CONCLUSION: In women with signs of preterm labor, the optimal work-up is CL measurement, and fFN testing in case of a CL between 15 mm and 30 mm, reducing unnecessary referrals and treatment.

Prognostic accuracy

Test strategy positive test if:	sensitivity	95% confidence interval	specificity	95% confidence interval	PPV	95% confidence interval	NPV	95% confidence interval
CL < 25 mm	0,93	0,86 - 0,97	0,56	0,51 -0,60	0,28	0,23 -0,33	0,98	0,95 - 0,99
CL < 30 mm	0,97	0,90 - 0,99	0,43	0,38 - 0,47	0,24	0,20 - 0,28	0,99	0,96 - 1,00
CL < 10 mm, or CL 10 - 30 mm and fFN+	0,90	0,81 - 0,94	0,69	0,64 - 0,73	0,35	0,29 - 0,41	0,97	0,95 - 0,99
CL < 10 mm, or CL 10 - 25 mm and fFN+	0,87	0,79 - 0,93	0,74	0,69 - 0,77	0,38	0,31 - 0,45	0,97	0,95 - 0,98
CL < 15 mm, or CL 15 - 30 mm and fFN+	0,92	0,84 - 0,96	0,67	0,62 - 0,71	0,34	0,28 - 0,40	0,98	0,96 - 0,99
CL < 15 mm, or CL 15 - 25 mm and fFN+	0,90	0,81 - 0,94	0,72	0,67 - 0,75	0,37	0,31 - 0,43	0,97	0,95 - 0,99
CL < 20 mm, or CL 20 - 30 mm and fFN+	0,92	0,84 - 0,96	0,60	0,56 - 0,64	0,30	0,25 - 0,36	0,98	0,95 - 0,99
CL <15 mm or fFN+	0,95	0,88 - 0,98	0,57	0,52 - 0,61	0,28	0,23 - 0,33	0,98	0,96 - 0,99
CL <20 mm or fFN+	0,95	0,88 - 0,98	0,50	0,45 - 0,54	0,27	0,22 - 0,32	0,98	0,95 - 0,99
CL <25 mm or fFN+	0,99	0,94 - 1,00	0,40	0,36 - 0,44	0,24	0,20 - 0,29	0,99	0,97 - 1,00
CL <30 mm or fFN+	1,00	0,96 - 1,00	0,32	0,28 - 0,36	0,22	0,18 - 0,26	1,00	0,98 - 1,00
CL <25 mm and fFN+	0,83	0,73 - 0,89	0,75	0,71 - 0,79	0,38	0,31 - 0,45	0,96	0,93 - 0,98
CL <30 mm and fFN+	0,85	0,76 - 0,91	0,70	0,66 - 0,74	0,34	0,28 - 0,41	0,96	0,94 - 0,98
fFN+	0,76	0,66 - 0,83	0,58	0,54 - 0,62	0,25	0,21 - 0,31	0,93	0,89 - 0,95

NPV, negative predictive value; *PPV*, positive predictive value.

12 Genetic variation associated with preterm birth in black women

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OBJECTIVE: Black race is one of the strongest risk factors for preterm birth (PTB). Recently published data supports the hypothesis that genetic variation is a critical component in the pathogenesis of PTB and may account, in part, for the differences in PTB among different racial groups. We sought to identify single nucleotide polymorphisms (SNPs) associated with PTB within a cohort of black women.

STUDY DESIGN: This is a secondary analysis of a randomized trial that evaluated the effect of periodontal disease treatment on PTB. Women were enrolled between 6-20 weeks gestation at three prenatal care clinics between 2004-2007. Maternal DNA samples were collected and analyzed using a custom 1536-SNP chip designed to specifically assess genes involved in inflammation. The association between PTB <37 weeks and PTB <34 weeks with each SNP was assessed among black women enrolled in the study (significance considered p<0.001). Dominant, codominant, additive and recessive inheritance models were considered. History of prior spontaneous PTB was controlled for in adjusted analyses.

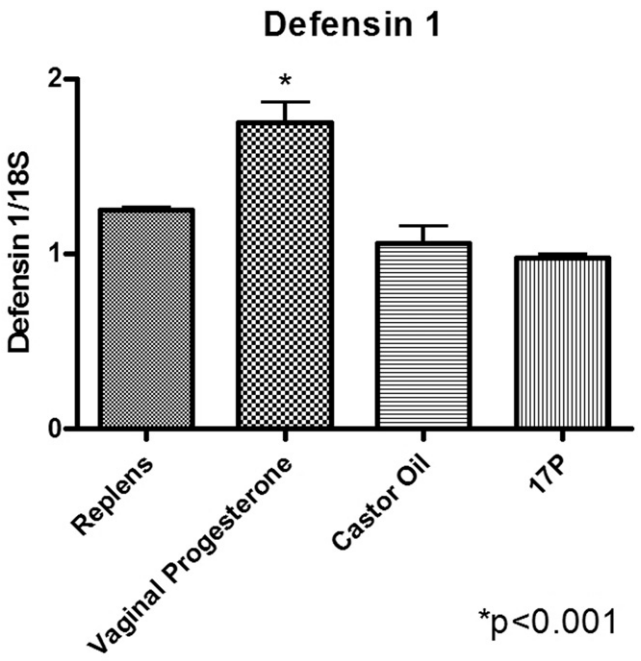
RESULTS: Of the 1,061 black women in the study with SNP data, 142 (13.4%) had a PTB <37 weeks gestation and 57 (5.4%) women delivered at <34 weeks gestation. Two SNPs in the PRKCA gene (rs6504424, rs7225452) as well as SNPs in the MMP2 gene (rs11639960) and C6 gene (rs6883180) were associated with an increased risk of PTB <37 weeks. A SNP in the IL17A gene (rs4711998) was found to be significantly associated with both PTB <34 weeks and <37 weeks. Additional SNPs in the PGR gene (rs11571275) and FLT1 gene (rs12428494) were associated with PTB <34 weeks but not <37

weeks. The only SNP protective against PTB was found in the IL3 gene (rs3091336).

CONCLUSION: We identified 8 novel SNPs in genes critical to inflammation, cell signaling, and angiogenesis that are associated with preterm delivery in black women. These genetic variants may be important in the pathogenesis of preterm birth, however further studies are needed to elucidate their precise role.

Gene	SNP	Outcome	Model	aOR † (95% CI)
Matrix metalloproteinase-2 (MMP2)	*rs11639960*	PTB <37 weeks	Recessive	6.76 (2.82-16.27)
Protein kinase C alpha (PRKCA)	*rs6504424* *rs7225452*	PTB <37 weeks PTB <37 weeks	Dominant Dominant	2.48 (1.50-4.12) 2.25 (1.44-3.50)
Complement component 6 (C6)	*rs6883180*	PTB <37 weeks	Recessive	2.22 (1.39-3.55)
Interleukin 3 (IL3)	*rs3091336*	PTB <37 weeks	Dominant	0.51 (0.36-0.74)
Interleukin 17A (IL17A)	*rs4711998*	PTB <37 weeks PTB <34 weeks	Recessive Recessive	1.99 (1.34-2.97) 2.76 (1.58-4.82)
Progesterone receptor (PGR)	*rs11571275*	PTB <34 weeks	Dominant	3.35 (1.66-6.79)
fms-related tyrosine kinase 1 (FLT1)	*rs12428494*	PTB <34 weeks	Additive	3.36 (1.69-6.70)

†All $P < .001$.



13 Prevention of preterm birth with progestational agents: revealing molecular mechanisms

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OBJECTIVE: Clinically, vaginal progesterone (Vag P) and 17 alpha-hydroxyprogestreone caproate (17P) have been shown to prevent preterm birth (PTB) in high risk populations. We hypothesize these agents may be preventing PTB by altering signal transduction pathways that would promote premature cervical remodeling. Specifically, we hypothesize that progestational agents modify the mucosal immune response in the cervix through altered production of TH17 cytokines and increased expression of anti-microbial proteins.

STUDY DESIGN: Using a mouse model, on days E14-E17 CD-1 pregnant mice were treated with either 0.1cc of 10mg/ml of 17P subcutaneously, 0.1cc of castor oil (CO) subcutaneously, 0.1 cc of 25 mg/ml of progesterone in Replens vaginally, or 0.1cc of Replens vaginally, with four dams per treatment group. Mice were sacrificed six hours after treatment on E17.5. Cervices were collected and quantitative real-time polymerase chain reaction (qPCR) was performed on the following targets: IL17, IL22, IL22R, Defensin 1, Defensin 3, Defensin 4, SLP1, and Claudin-2.

RESULTS: Exposure to Vag P significantly increased the expression of Defensin 1 compared to Replens ($p<0.01$), CO ($p<0.001$), and 17P ($p<0.001$). Vag P also significantly increased expression of IL22R compared to CO ($p<0.05$) and 17P ($p<0.05$). Treatment with either 17P or Vag P did not have a statistically significant effect on the production of SLP1, or Claudin-2. Baseline mRNA values of IL17, IL22, Defensin 3, and Defensin 4 levels were very low; expression was not altered by any of the treatments.

CONCLUSION: These studies demonstrate that progesterone administered vaginally can alter the musical immune response. Notably, Vag P, through an increase in Defensin 1 and IL22R expression, served to boost the host mucosal immune response in the cervix. Whether these molecular changes from Vag P result in a functional effect and are a key mechanism by which Vag P prevents PTB requires further study. Importantly, 17P had no effect on these pathways in the cervix.

14 Extravillous trophoblasts within the placental basal plate serve as a protected niche for intracellular bacterial reservoirs: potential new etiology for preterm birth

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OBJECTIVE: Infection and inflammation are important mechanisms contributing to Preterm birth (PTB). However, the mechanism by which pathogens infect and induce pathological change during pregnancy remains unknown as does the contribution of latent and chronic infection. Antibiotic treatment is relatively ineffective for preventing PTB suggesting that the putative infectious organisms may be 'hidden' within the tissue. Our central hypothesis is that one cause of PTB is that bacterial pathogens establish clinically occult reservoirs in fetal extravillous trophoblasts (EVTs) on the maternal side of the placenta (basal plate).

STUDY DESIGN: Placental basal plate biopsies were collected from n=200 women with PTB <37 weeks and controls ≥37 weeks, stained with the Brown-Hopps modification of the Gram-stain and examined for intracellular bacteria. To explore the mechanisms underlying formation of intracellular bacterial reservoirs, ex vivo human basal plate explants were developed and infected with Gram-negative. (Uropathogenic E. coli, UPEC) and Gram-positive (Listeria monocytogenes) pathogens.

RESULTS: Intracellular bacteria were documented in over a third of preterm placentas and were exclusively localized to fetal EVTs (Figure 1A-B). We show that both UPEC and Listeria invade into HLA-G+ EVTs embedded within the basal plate. Bacteria appear to hone directly to fetal EVTs and not maternal stromal cells. Interestingly, UPEC appear to form biofilm-like clusters in EVTs whereas Listeria remain as single organisms (Figure 1C-D).

CONCLUSION: Our work has thus demonstrated that EVTs are highly susceptible to bacterial invasion and colonization likely due to their unique immune-privileged status. We show that Gram positive and negative bacteria may use different mechanisms to persist. We posit that such reservoirs persisting within EVTs in the basal plate could re-emerge and predispose to adverse pregnancy outcomes such as PTB.