

Thursday, January 26 • 1:15 PM - 4:00 PM • Augustus I-II

## PREMATURITY

## Abstracts 9-19

Moderators: Jay Iams, MD; Joe Simpson, MD, Senior Vice President for Research and Global Programs, March of Dimes

**9 Progesterone promotes the expansion of proangiogenic immature myeloid cells and prevents their differentiation into inflammatory cells**Ofer Fainaru<sup>1</sup>, Gili Paz<sup>1</sup>, Shay Hantisteanu<sup>1</sup>, Rivi Hertz<sup>1</sup>, Shahar Kol<sup>1</sup>, Zeev Weiner<sup>2</sup><sup>1</sup>IVF Unit and Laboratory for Reproductive Sciences, Rambam Medical Center, Haifa, Israel, <sup>2</sup>IVF Unit Department of Obstetrics and Gynecology, Haifa, Israel

**OBJECTIVE:** Immature myeloid cells (IMCs) are bone marrow-derived cells that normally differentiate into granulocytes, macrophages, and dendritic cells (DCs) but expand in pathological conditions such as malignancy. DCs are antigen-presenting cells that regulate the immune response. We have shown that IMCs accumulate in the placenta and actively promote angiogenesis. IMCs peak in concentration during mid-pregnancy and their presence correlates with neonatal birthweight. Furthermore, labor and delivery are preceded by a decrease in IMCs and an increase in DCs populating the placenta. We hypothesized that progesterone may promote IMC population expansion while preventing their differentiation into inflammatory cells.

**STUDY DESIGN:** We derived bone marrow cells from C57Bl6 pregnant mice. We isolated the CD11b<sup>+</sup> myeloid subset by magnetic based immuno-separation, and cultured them in the presence of GM-CSF and progesterone (10<sup>-7</sup>, 10<sup>-8</sup>, and 0 mM). After 5 days we analyzed cultures for the presence of Ly6C<sup>int</sup>Ly6G<sup>hi</sup> granulocytic IMCs, Ly6C<sup>hi</sup>Ly6G<sup>int</sup> monocytic IMCs and CD11c<sup>+</sup>MHCII<sup>+</sup> DCs by flow cytometry. We also compared their presence in Lewis Lung Carcinoma tumors that were implanted subcutaneously in mice to that in placentas derived from pregnant mice.

**RESULTS:** Progesterone treatment caused a dose dependent increase in granulocytic IMCs (n=3, p<0.05), accompanied by a concomitant decline in the monocytic IMCs (n=3, p<0.001). Importantly, these changes were paralleled by a decrease in DCs (n=3, p<0.05). When analyzing CD45<sup>+</sup> hematopoietic cells in tumors and placentas, we detected a significant enrichment (P<0.01) of monocytic IMCs subpopulation in tumors compared to that in placentas. This was paralleled by a concomitant, more than 2-fold decrease (P<0.01) in granulocytic IMCs.

**CONCLUSION:** Progesterone enhances proliferation and/or survival of placenta specific- granulocytic IMCs but not that of tumor specific-monocytic IMCs, in a dose dependent manner. Importantly, the differentiation of IMCs into DCs was abrogated by progesterone. We thus speculate that progesterone may play role in the maintenance of proangiogenic IMCs in the placenta. Inhibition of their differentiation into inflammatory cells such as DCs and neutrophils might explain, at least in part, the protective effect of progesterone in preventing preterm labor.

**10 Distinct microbiota in the cervicovaginal space are associated with spontaneous preterm birth: findings from a large cohort and validation study**Michal Elovitz<sup>1</sup>, Pawel Gajer<sup>2</sup>, Katheryne Downes<sup>1</sup>, Jacques Ravel<sup>2</sup><sup>1</sup>University of Pennsylvania, Philadelphia, PA, <sup>2</sup>University of Maryland, Baltimore, MD

**OBJECTIVE:** Changes in microbial communities have been implicated in both health and disease. Investigations into the association between the cervicovaginal (CV) microbiota and spontaneous preterm birth (SPTB) have been limited in scope and number. This study sought to assess if longitudinal cohort of pregnant women and then to perform validation in a 2<sup>nd</sup> prospective cohort.

**STUDY DESIGN:** A prospective cohort of singleton pregnancies were enrolled ("M&M", n=1500). Biospecimens were collected at 3 time points in pregnancy (16-20 (V1), 20-24 (V2), 24-28 (V3) weeks). All cases of PTB were adjudicated by the PI. From the larger cohort, a nested case-control was performed with 80 SPTB cases and 320 term controls that were frequency matched by race to the cases. 16S rRNA gene analyses were performed to characterize the composition and structure of the CV microbiota. The effect of bacteria was quantified as the log ratio between the mean relative abundance at SPTB samples vs. TERM delivery samples. The log ratios were estimated using zero-inflated negative binomial models. A second cohort of woman ("STOP") with specimens collected between 22-32 weeks was used as validation (N=616).

**RESULTS:** When performing phylotype analyses, 127 phylotypes were detected in all samples from both cohorts. Significant associations were demonstrated between specific bacteria, in both a positive and negative manner, with SPTB. 37 bacteria were significantly associated with a decreased risk of SPTB while 13 were associated with an increased risk in the primary cohort. Racial differences in these associations were evident (figure 1). The validation cohort confirmed the highly significant associations between specific microbes and SPTB. Bifidobacterium species were noted to be significantly protective against SPTB at all gestational time points while BVAB2, BVAB3 and Mobiluncus were associated with a dramatic increase risk of SPTB (all q-values <0.0001).

**CONCLUSION:** CV microbiota are significantly associated with SPTB. Targeting the bacteria that are associated with an increased risk of SPTB and/or enhancing the presence of the protective bacteria may serve as new therapies to reduce the rate of PTB. With this new evidence, these types of studies should become a research priority. (R01NR014784).

