Systemic Inflammation in Pregnant Women with and without Latent Tuberculosis Infection

Shilpa Naik[1,2], Mallika Alexander[1], Pavan Kumar[3], Vandana Kulkarni[1], Su Yadana[4], Ramesh Bhosale[1,2], Subash Babu[3], Amita Gupta[1,5] Jyoti Mathad[6] and **Rupak Shivakoti[4]**

Institutions: [1]Byramjee-Jeejeebhoy Government Medical college-Johns Hopkins University Clinical Research Site, Pune, India, [2]Byramjee Jeejeebhoy Government Medical College, Pune, India, [3]National Institutes of Health, National Institute for Research in Tuberculosis, International Center for Excellence in Research, Chennai, India, [4]Columbia University Mailman School of Public Health, New York, USA, [5]Johns Hopkins University School of Medicine, Baltimore, USA, [6]Weill Cornell Medical College, New York, USA. E-mail: rs3895@cumc.columbia.edu

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Intro

Recent studies show increased systemic inflammation in adults with latent tuberculosis infection (LTBI+) compared to those without (LTBI-)

Potential differences in systemic inflammation by LTBI status has not been assessed in pregnant women

It is also not know whether potential differences in systemic inflammation during pregnancy is linked to the increased progression of TB observed in pregnant and postpartum women

The objective of this study was to address this research gap and determine potential differences in systemic inflammation by LTBI status
An secondary objective was to explore the association of systemic inflammation with TB progression

Methods

We conducted a cohort study of 155 LTBI+ and 65 LTBI- pregnant women, stratified by HIV status attending an antenatal clinic at BJ Medical College in Pune, India

Women were enrolled in second or third trimester, and had their LTBI status assessed by IRGA test

Plasma samples was used to measure markers of systemic inflammation through immunoassays: IFNβ, CRP, AGP, I-FABP, IFNγ, IL-1β, sCD14, sCD164, TNFα, IL-6, IL17a and IL-13

Univariable and Multivariable linear regression models were fit to test the association of LTBI status with each inflammation marker

Results

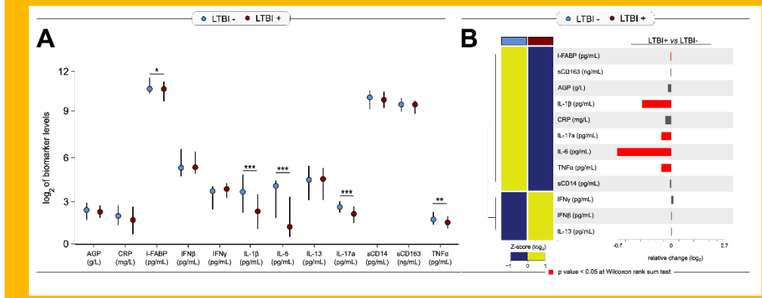

Figure 1: Levels of third trimester inflammation by LTBI status (N=220)

Legend: A) Median and interquartile range (IQR) Log_2 levels of markers, measured in the 3rd trimester is shown for LTBI+ (n=155) and LTBI- (n=65) pregnant women. Wilcoxon rank-sum test was used to calculate p-values. *p < 0.05, **p < 0.01 and ***p < 0.001. B) Relative fold-change is shown for each marker by LTBI status. Red bars indicate p-value < 0.05.

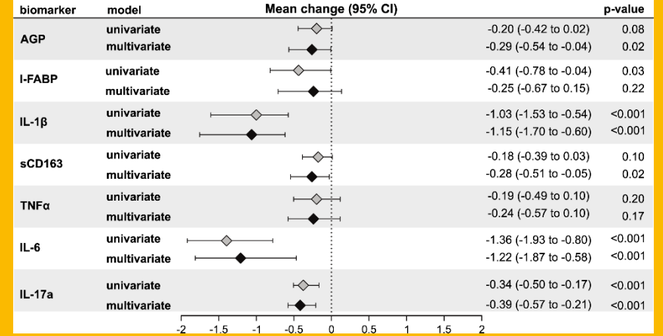

Figure 2: **Association of LTBI status with third trimester inflammation (N=220)**

Legend: Using linear regression, the mean change in Log_2 concentrations of each inflammation marker and 95% confidence intervals (95% CI) among LTBI+ individuals compared to LTBI- individuals is shown in the forest plot. Inflammation markers were measured in samples collected at the third trimester of pregnancy. Multivariate models adjusted for age, MUAC, HIV status, diet and gestational diabetes status. Only immune markers with a p-value <0.2 in the univariate model are shown.

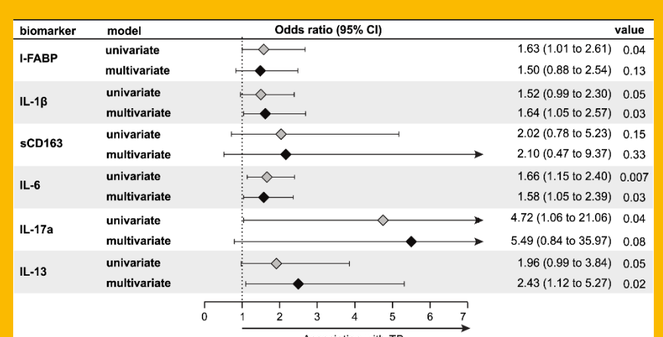

Figure 3: **Association of third trimester inflammation markers with TB progression (N=155; 9 progressors)**

Legend: Using logistic regression, the odds ratio and 95% CI of TB progression per log_2 increase in each inflammation marker among LTBI+ pregnant women is shown in the forest plot. Progressors were defined as those who developed TB either during pregnancy (n=1) or post-partum (n=8). Inflammation markers were measured at the third trimester. Multivariable models adjusted for age, MUAC and HIV status.

Results and Discussion

Results:

- Study population characteristics were a median age of 23, 28% undernourished, 25% with less than secondary education, 7% with gestational diabetes and 32% with HIV (by design)
- In multivariable models, LTBI+ women had significantly lower levels of **second** trimester AGP, I-FABP, IL1β, IL-6 and IL17a, and higher levels of IFNγ compared to LTBI- women
  - AGP, IL1β, IL-6 and IL17a results were robust to Bonferroni corrections
- LTBI+ also had significantly lower levels of **third** trimester AGP, IL1β, sCD163, IL-6 and IL-17a
  - IL1β, IL-6 and IL-17a results were robust to Bonferroni corrections
- In exploratory analysis, there was a significantly increased odds of progression among LTBI+ pregnant women per log_2 increase in third trimester plasma levels of IL-1β, IL-6 and IL-13 in multivariable models

Discussion:

- Interestingly, LTBI+ pregnant women had lower levels of various inflammatory cytokines in both the second and third trimester of pregnancy compared to LTBI- women
- Future studies in diverse settings should confirm these findings and also assess potential mechanisms
- Impact of these findings are not clear but our exploratory data analysis suggests that the systemic immune profile might be linked to progression of TB in pregnancy and postpartum
  - Future larger studies will need to confirm this
  - If confirmed, this profile could identify subsets of LTBI+ women at higher risk of TB progression
- In summary, we identify a unique systemic immune profile in LTBI+ pregnant women