Elevated interferon-gamma levels during pregnancy are associated with adverse maternofetal outcomes in IBD

We read with interest van der Giessen's observations of pregnancy-associated fluctuations in peripheral blood cytokines and stool microbiota in the setting of IBD.[1] In this study, the authors profiled preconception and pregnancy-associated cytokine levels and demonstrated a significant decrease in proinflammatory cytokines (interleukin (IL)-6, IL-8, IL-12, IL-17 and tumour necrosis factor-α) during pregnancy in women with IBD.

We had undertaken a similar cytokine analysis of pregnant women with IBD at the University of Calgary but sought to relate preconception and second-trimester cytokine levels with adverse maternal–fetal outcomes, including preterm birth, emergency caesarean delivery and neonatal intensive care unit (NICU) admission. Sera from 28 women with IBD, including 19 with Crohn's disease (CD) and 9 with UC who completed a pregnancy between 2013 and 2015, were analysed. Eighteen of these patients were on biological therapy preconception (infliximab n (CD)=7, n (UC)=4; adalimumab n (CD)=7). Disease activity was prospectively evaluated using validated disease activity indices, physician global assessment and C-reactive protein. Faecal calprotectin results were not available. Only one patient (with CD) had active disease at the time of preconception blood sampling, while three women (1 with CD and 2 with UC) had a disease flare during pregnancy. Of those with an intrapartum disease flare, one patient with UC was commenced on infliximab in trimester 1 (between the two blood draws), and one patient with CD was commenced on infliximab after the second-trimester blood draw. All patients continued biological therapy beyond the second-trimester blood draw.

Similar to van der Giessen *et al*, we observed a significant pregnancy-associated decrease in proinflammatory (Th1 and Th17) cytokines, namely, IL-17A, IL-21, IL-23 and interferon (IFN)-γ between the preconception period and trimester 2. A similar pattern was not observed in patients with UC, perhaps owing to the low baseline cytokine levels observed in this smaller cohort (figure 1).

Preterm birth, defined by delivery prior to 37-week gestation, occurred in five women, all with CD. There was no significant decrease in IFN-γ levels across the pregnancy in the women who had a preterm delivery compared with women who had a term birth ($p=0.625$ and $p=0.022$, respectively; figure 2B). The lack of association between proinflammatory cytokines and preterm birth (gestational age <37 weeks) in our cohort might reflect the average gestation of 36 weeks and 2 days in four of the preterm infants, with only one gestation fulfilling the definition of an extremely preterm birth (<32 weeks).

Importantly, 11 women underwent an emergency caesarean delivery, and five newborns required NICU admission. IFN-γ levels were significantly higher in trimester 2 in the 11 women who proceeded to an emergency Caesarean delivery compared with the 17 patients

who had a vaginal or elective caesarean delivery (p=0.020, figure 2A). Of the 29 newborns (there was 1 twin gestation), 5 were admitted to the NICU (including 1 who was delivered preterm), of which 4 were emergency caesarean deliveries. Higher preconception and second-trimester IFN-γ levels were associated with NICU admission (p=0.036 and p=0.022, respectively; figure 2C).

Although we were unable to identify a cytokine 'signature' that could reliably predict maternal–fetal outcomes, the canonical proinflammatory cytokine, IFN-γ, was most associated with adverse outcomes in our cohort. Bröms *et al* demonstrated that active disease during pregnancy is a primary driver of preterm delivery in women with IBD, which is concerning, given that preterm birth remains the leading cause of neonatal morbidity and mortality globally.[2] Furthermore, elevated Th1 cytokines have been associated with recurrent pregnancy loss as well as implantation failure during in vitro fertilisation.[3–5] Suppressing clinical and subclinical inflammations during pregnancy likely remains key to optimal maternal–fetal outcomes for patients with IBD. However, other yet to be identified IBD-related factors may drive adverse outcomes independent of cytokine and disease activity. Future studies examining the composite contribution of host and environment to disease course and pregnancy outcomes (eg, microbiome or metabolome profiling) are therefore warranted.

Given, the rich data source available to van der Giessen *et al*, we invite the authors to comment on the relationship between serum cytokine levels and maternal–fetal outcomes in their cohort.

Humberto Jijon ,[1] **Aito Ueno**,[1] **Nastaran Sharifi**,[1] **Yvette Leung**,[2] **Subrata Ghosh**,[3] **Cynthia H Seow**[1]

[1]Department of Medicine, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada
[2]Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[3]Institute of Translational Medicine, University of Birmingham Edgbaston Campus, Birmingham, UK

Correspondence to Dr Cynthia H Seow, Department of Medicine, University of Calgary, Calgary, AB T2N 1N4, Canada; cseow@ucalgary.ca

Correction notice This article has been corrected since it published Online First. The last author's name has been corrected.

Contributors HJ, AU, NS, YL, SG and CS contributed to the study design, data collection, data analysis, manuscript drafting and editing.

Funding This study was funded by Alberta Innovates Health Solutions.

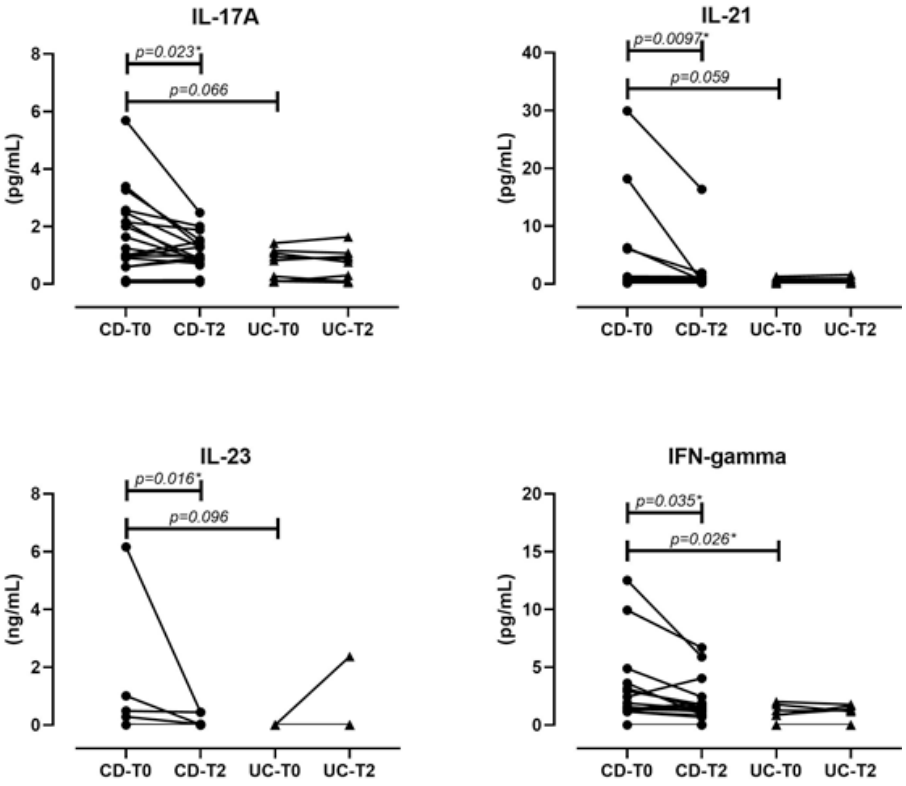

Figure 1 Serum levels of proinflammatory cytokines (IL-17A, IL-21, IL-23 and IFN-γ) decreased following conception. Comparisons of individual cytokines between patients with CD and UC for preconception and trimester 2 are shown. Significant differences between the two time points were analysed by Wilcoxon signed-rank test, while significant differences between CD and UC were analysed by the Mann-Whitney test. Note that most patients with UC had undetectable IL-23 levels, hence the overlap. CD, Crohn's disease; IFN, interferon; IL, interleukin.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

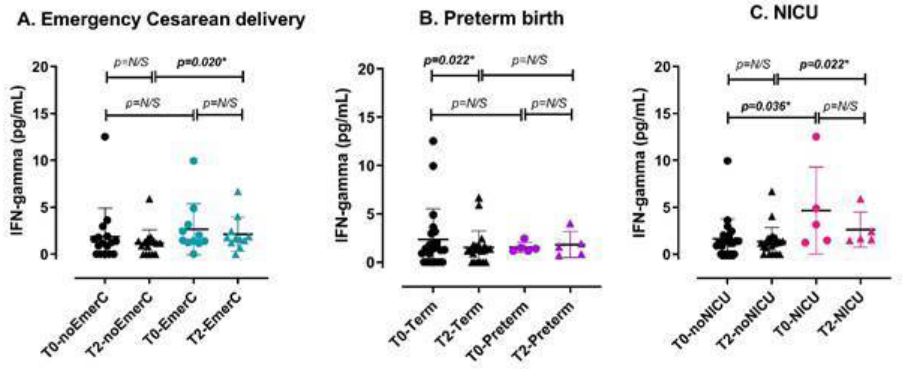

Figure 2 Serum levels of IFN-γ were associated with adverse maternal-fetal outcomes in our cohort. (A) comparison of IFN-γ levels between noEmerC (n=17) versus EmerC (n=11) for T0 and T2. (B) Comparison of IFN-γ levels between patients who delivered term (n=23) and preterm (n=5) for T0 and T2. (C) Comparison of IFN-γ levels between noNICU (n=23) and those that were admitted to NICU (n=5) for T0 and T2. Significant differences for T0 and T2 were analysed with the Wilcoxon signed-rank test, while significant differences between maternal–fetal outcomes were analysed by Mann-Whitney test. EmerC, patients who underwent an emergency caesarean delivery; IFN, interferon; NICU, neonatal intensive care unit; noEmerC, patients who did not undergo an emergency caesarean delivery; noNICU, patients whose newborn babies did not require NICU admission; T0, preconception; T2, trimester 2.

To cite Jijon H, Ueno A, Sharifi N, *et al*. *Gut* 2020;**69**:1895–1897.

Received 15 August 2019
Revised 29 October 2019
Accepted 30 October 2019
Published Online First 13 November 2019

Gut 2020;**69**:1895–1897. doi:10.1136/gutjnl-2019-319656

ORCID iD
Humberto Jijon http://orcid.org/0000-0003-2270-0625

REFERENCES

1 van der Giessen J, Binyamin D, Belogolovski A, *et al*. Modulation of cytokine patterns and microbiome during pregnancy in IBD. *Gut* 2019
2 Bröms G, Granath F, Stephansson O, *et al*. Preterm birth in women with inflammatory bowel disease - the association with disease activity and drug treatment. *Scand J Gastroenterol* 2016;51:1462–9.
3 Abdolmohammadi Vahid S, Ghaebi M, Ahmadi M, *et al*. Altered T-cell subpopulations in recurrent pregnancy loss patients with cellular immune abnormalities. *J Cell Physiol* 2019;234:4924–33.
4 Azizi R, Ahmadi M, Danaii S, *et al*. Cyclosporine A improves pregnancy outcomes in women with recurrent pregnancy loss and elevated Th1/Th2 ratio. *J Cell Physiol* 2019;234:19039–47.
5 Kwak-Kim JYH, Chung-Bang HS, Ng SC, *et al*. Increased T helper 1 cytokine responses by circulating T cells are present in women with recurrent pregnancy losses and in infertile women with multiple implantation failures after IVF. *Hum Reprod* 2003;18:767–73.