**Author’s response to reviews**

**Title:** Association of a placental Interleukin-6 genetic variant (rs1800796) with DNA methylation, gene expression and risk of acute chorioamnionitis

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Responses to reviewers comments:

Comment #1) Although authors stated that potential variables that might affect the results such as socio-economic status, maternal smoking and alcohol use, PPROM status were not documented for all patients, these information should be collected retrospectively and statistical analysis should be accounted.

Response: While this would be desirable, many of the cases were obtained as deidentified samples (as mentioned in our Declarations), and we do not have the ability to get this information. The aCA cases and non-aCA cases were sampled from a single urban population (Vancouver) and delivering at a single centre--BC Children’s & Women’s Hospital--which is located in a relatively high socio-economic status neighborhood. Of the 80 documented observations for maternal smoking status, almost all of the cases (79/80) identified themselves as non-smokers. Additionally, the most reproducible finding between maternal smoking and altered DNAm is observed at sites linked with AHRR and CYP1A1. We therefore tested for differences at these sites and did not observe altered DNA methylation associated with our pathology at these sites in our study cohort.

This information is now added to the manuscript (Methods, line number 109-115).

Comment #2) Conclusion part of both abstract and manuscript should be clearer.

Response: We have now edited our abstract and manuscript conclusions.

**Manuscript Conclusion (Line number 375-383)**

"Our findings suggest that a placental (fetal) CC genotype at the IL6 SNP (rs1800796), which is largely limited to individuals of East Asian ancestry, is associated with aCA. Placentas with the CC genotype..."
exhibited increased DNA methylation at multiple CpG sites upstream and within IL6, as compared to those of GG genotype. This increased DNA methylation was associated with lower expression of IL6 and with aCA status. While overexpression of IL6 is associated with various inflammatory conditions, this can be a consequence of infection; whereas, innate IL6 deficiency can lead to impaired immunity against microbial infection. Taken together, we conclude that IL6 genetic polymorphisms may influence susceptibility to aCA by affecting the risk of acute infection. Larger samples sizes are needed to confirm these findings."

Abstract Conclusion (Line number 24-29)
"We demonstrated that the minor C allele at the IL6 SNP (rs1800796), which is largely limited to East Asian populations, is associated with the presence of aCA. This SNP was associated with increased DNAm at a nearby MEPC2 binding site, which was in turn associated with decreased expression of IL6 in the placenta. Decreased expression of IL6 may increase vulnerability to microbial infection. Additional studies are required to confirm this association in Asian populations with larger sample sizes."

Comment# 3) Title of the manuscript should be re-edited.
Response: We have now edited the title of the manuscript

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