Reviewer's report

Title: Quantifying circulating hypoxia-induced RNA transcripts in maternal blood to determine in utero fetal hypoxic status

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Reviewer: Dean Myers

Reviewer's report:

This manuscript by Clare Whitehead and colleagues describes the circulating RNA pattern in maternal and fetal (cord) blood at term in either induced labor in uncompromised pregnancies or in pregnancies with a severely growth restricted fetuses (<10th percentile). In addition, they authors determined quantitative differences in key hypoxia related RNAs in both maternal and fetal blood in these both acute hypoxic (induced) and chronic hypoxic (IUGR/FGR) pregnancies. The overall concept that circulating RNAs (mRNA) would change in response to either acute or chronic hypoxia is novel and innovative. Indeed, these RNA species have the potential to effect both maternal and fetal systems in an adaptive or maladaptive manner in response to the hypoxia, in addition to providing a means to identify potential fetuses that had been exposed to either chronic or acute hypoxic bouts in utero. Hypoxia is one of the most common of fetal perturbation. The methods- use of microarrays and qRT-PCR validation- appear adequate and appropriate. The findings of changes in key hypoxic associated mRNAs is exciting and is of broad interest to the field.

Some concerns do however need addressing:

MAJOR:

1) The cutoff for fetal hypoxia (lactate <4 mmol/L) needs defining. Why this cutoff?

2) In the FGR group, preeclamptic pregnancies were included. While preeclampsia is known to lead to chronic fetal hypoxia, in itself, preeclampsia may alter placental miRNA/mRNA patterns independent of fetal hypoxia. This group should be evaluated separately.

3) A table need to be included with fetal pO2, lactate values for control, induced and FGR pregnancies. Or in graphical form with both hypoxic and normox fetuses depicted. It would seem appropriate to also separate preeclamptic and smoking from the uncomplicated FGR. As per smoking: these pregnancies (a small number) would seem to need to be excluded since smoking induces both FGR, fetal hypoxia but also nicotine effects independent of hypoxia.

4) In addition to pre-pregnancy diabetes, maternal obesity could also impact the pattern and level of mRNAs. Obesity is associated with an inflamed placenta and potential reduced placental function. The authors should consider obese pregnancies as an independent group to evaluate the contribution of obesity vs hypoxia per se, or the combination of obesity and hypoxia.
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests