Reviewer’s report

Title: Maternal iron metabolism gene variants modify umbilical cord blood lead levels by gene-environment interaction: a birth cohort study

Version: 1
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Reviewer: Claudia Gundacker

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Karwowski and colleagues investigated the relationship between iron metabolism gene variants (HFE and TF missense mutations) and lead concentrations in maternal blood and umbilical cord blood. Our knowledge about genetic influences on lead toxicokinetics at the maternal-fetal interface is extremely poor. This study provides new data based on methods that are well described and appropriate. The data are sound and sufficiently controlled.

Major compulsory revisions:

There remain concerns on the interpretation and evaluation of the results. The Discussion section is inconclusive. In the Introduction section more basic information should be provided.

Several aspects are inadequately addressed concerning what has been found, i.e., maternal HFE genotype has stronger effects on cord blood lead concentrations than infant HFE genotype:

- A brief introduction into the HFE-282 mutation and how it affects iron and lead metabolism is missing, although it is stated on page 16 that HFE C282Y is a well characterized functional variant.

The „unique physiological state of pregnancy“ (page 5, third par.) is not described further.

Also the complex situation at the maternal-fetal interface has not been thought through regarding

- genetics: the placenta is fetal tissue/genotype
- the „metal transport machinery“ (pages 9, 14). The only information provided on that „machinery“ is that „HFE protein influences the expression of ...DMT1“ (page 5, sec. par), which in turn „mediates lead absorption in the intestine“ (page 14, sec. par). It remains unexplained in which way HFE modulates DMT1 levels and at which level (RNA, protein?). Where is the link to the HFE mutations?
- localization of the involved transporters/receptors in the placenta layers together with the direction of transport [citations 36, 37 or e.g., Parkkila et al. (1997). Association of the transferrin receptor in human placenta with HFE, the protein defective in hereditary hemochromatosis. Proceedings of the National Academy of Sciences, 94(24), 13198-13202].
Metallothioneins are not transporters (page 14, sec.par.) but ligands for divalent metal cations and thus involved in metal storage and detoxification.

An explanation for the circumstance that placentas were not collected and analysed is missing. To know serum iron levels of mother-child dyades would also have increased the significance of the study.

Level of interest: An article of importance in its field

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