Reviewer's report

Title: Brain iron accumulation in unexplained fetal and infant death victims with smoker mothers - The possible involvement of maternal methemoglobinemia

Version: 1 Date: 14 December 2010

Reviewer: Nadja W Schroder

Reviewer's report:

The article by Lavezzi et al., presents interesting data on brain iron accumulation found in fetal and infant death victims. The finding that iron accumulates in the brains of fetuses and infants victims is interesting by itself.

Major Compulsory Revisions

The main problem is the interpretation given by the authors in order to explain such findings. They correlate this finding with the smoking habit of the mothers. In fact, most of the victims presenting iron accumulation were from the group of smoking mothers, while no iron accumulation was found in the group of victims coming from non smoking mothers. They hypothesize that maternal oxidative Hb damage induced by nicotine could lead to Fe+3 release in maternal blood which would readily cross the placental barrier and accumulate in the fetal blood and brain, inducing hypoxia. This hypothesis is not supported by the data, since the authors do not provide information on maternal Hb.

Other possible explanations should be included in the Discussion of the manuscript. There are more complex interrelations involving iron homeostasis in the fetus and the neonate that could be involved in iron accumulation in brain regions. For instance it is known that iron homeostasis is regulated by a complex interaction of iron regulatory proteins and that this system may not be matured in fetus and infants.

Another plausible explanation could be the diffusion of oxidants present in the smoke to the fetal tissues that could damage fetal Hb itself causing iron misregulation. Accordingly, some studies show that neonatal erythrocytes are more likely to release free iron.

As the authors state in the 10th paragraph of the Discussion, iron accumulation has been implicated in the pathogenesis of neurodegenerative disorders. Remarkably, the mechanisms that lead to iron accumulation are not completely understood. Therefore, one cannot rule out the possibility of unknown mechanisms that could result in brain iron accumulation in newborn and infant victims of unexplained death. The authors should further discuss these different explanations for the present findings.

The Results section describes qualitative analysis of iron deposition in brain regions of the victims, which is shown in the Figures 1-7.

The authors should clarify the statistical analysis performed and the quantitative
analysis. In the Materials and Methods sections it is stated that ANOVA analysis of variance was used, but no data is presented in relation to this analysis in the Results section. In fact, they state that there is a “..highly significant correlation between maternal smoking and alterations in brain iron homeostasis”. Which statistical test was used to indicate this correlation? ANOVA does not indicate correlation, a proper test should be applied. Please clarify and include quantitative data.

Minor Essential Revisions
In the last sentence of the Background section it is stated that “…brain tissues of victims of unexplained death, aged from 22 gestational weeks to…”. However, in the first sentence of Methods it is informed 25-40 gestational weeks. Please indicate the correct time point.

Abbreviations should be defined the first they are used. For instance, ANS, SIDS, SIUD.

**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.