Commentary: Mercury, PCB, and now eicosapentaenoic acid: still another reason why pregnant women should be concerned about eating seafood?

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Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are collectively described as marine fatty acids since they derive mainly from marine food sources. They are believed to protect against cardiovascular diseases and perhaps also prostate cancer and rheumatoid arthritis. With regard to pregnancy and the perinatal period, there is evidence from randomized controlled trials that they may have the potential to prevent preterm birth, and DHA is known to be essential to early neurodevelopment.

In a paper in this issue Grandjean et al.1 conclude that consumption of relatively high amounts of EPA in pregnancy may have a negative impact on fetal growth. The study is based on 179 pregnancies in the Faroe Islands. Maternal samples taken in gestation week 34 were analysed for fatty acids in serum and PCB compounds (a group of organochlorines) and mercury in whole blood, whereas umbilical samples were analysed for serum fatty acids and whole blood mercury, but not for PCBs. The availability of all these measurements for the same individuals makes this study unusual, and the authors use their data to try to disentangle possible effects of the different substances on fetal growth and gestation length. The authors’ own emphasis is on their finding of an inverse relationship at birth between an infant’s weight and its serum level of EPA. In a multiple linear regression model, this association held after adjustment for mercury, also quantified in fetal blood at birth, and for a summary measure for 28 different PCB compounds, quantified in maternal blood obtained in week 34 of gestation.

The worrying conclusion that EPA in high amounts may inhibit fetal growth may however be the least plausible among several alternative explanations of these results. The consumed quantities of the substances in question—fatty acids, mercury and PCBs—are not the only determinants of the corresponding biochemical measures quantified in the bloods. This gets particularly problematic when a cross-sectional design is employed. The inverse association described between fetal growth and EPA could, for instance, be due to heavy fetuses catabolizing larger EPA quantities than lighter fetuses of same age. The authors state that similar but weaker associations were seen when EPA was quantified in maternal blood in week 34 of gestation rather than in the umbilical blood. However, in principle the same problem persists since infants heavy for gestational age at birth are already likely to be relatively heavy fetuses at 34 weeks, and several earlier studies have suggested that the fetus drains the mother’s stores of essential fatty acids, e.g. ref. 2.

Interestingly, differences were found between DHA and EPA in patterns of association. DHA (thus corroborating findings from randomized controlled trials with fish oil3,4) but not EPA, was directly associated with gestation length and EPA (as mentioned), but not DHA, was inversely associated with the measure for fetal growth rate. The authors interpret this as indicating that consumed quantities of EPA and DHA differ in their effects on these outcomes, an interesting possibility that deserves scrutiny in future studies. However, again, these patterns may just as well reflect possible differences in metabolism of these two fatty acids.

Neither is the conclusion that EPA must be the culprit, because the association was unaffected by adjustment for seafood pollutants, a quite straightforward one. Thus, ‘both PCB and methyl mercury exposure biomarkers are likely to be imprecise indicators of the causative concentrations, thereby resulting in attenuated regression coefficients’ (citation from one of the authors’ other papers5). Indeed, serum EPA, despite being potentially influenced by metabolic factors, may even be a more accurate proxy for the possible underlying causative pollutant than the employed PCB and mercury biomarkers. Finally, as a corroboration of their contention, the authors cite rat studies that showed reduced birthweights after fish oil supplementation in pregnancy.6,7 However, another explanation of those findings was the reduced gestational weight gain and the reduced caloric intake observed in rats fed ad libitum on a diet mixed with fish oil.6

This discussion has a much wider perspective. Many pregnant women in Europe and North America associate seafood with something that could cause harm to their fetuses. The concern has primarily focused on the possible detrimental effects of seafood pollutants, particularly mercury and PCBs, on early neurodevelopment. While the concern raised here about EPA in seafood may not be warranted, if only based on the above evidence, the pollutant issue should be taken very seriously. The epidemiological evidence for an effect of mercury stems primarily from two follow-up studies (here disregarding evidence from pollution disasters). One study, also conducted by Grandjean et al., reported an inverse association between fetal mercury exposure, measured at birth, and tests of memory, attention, and language in Faroese children up to 7 years of age.8 Several other measures, like motor function and visual spatial ability, tested negative, however. These findings were at variance with
findings from the study conducted in the Seychelles, where mercury exposure is also high due to high fish consumption.\(^9\) In that cohort none of the employed fetal mercury exposure measures were significantly associated with adverse developmental effects or with IQ measures in school-age children up to 66 months of age.

A particularly delicate aspect of the discussion is the question of whether populations that have traditionally subsisted on fish and sea mammals should decide to reduce their intake from these sources for health reasons. The Faroese authorities have issued official recommendations to limit fetal exposure to seafood pollutants; probably much based on the findings in the Faroese cohort.\(^8\) Women planning pregnancy are advised to stop eating whale meat at least 3 months before pregnancy, whilst women of reproductive age and girls are advised to abstain totally from eating whale blubber. On the contrary, the health authorities in Greenland, where marine mammals also play a central role in the diet, have so far decided not to issue any official recommendations on the basis of existing knowledge.

Such recommendations are warranted if the associations seen in the Faroese data between mercury and neurodevelopmental indices truly reflect causality. Judging the strength of the evidence in the Faroese data between mercury and neurodevelopmental outcomes expected to have different confounder constellations. For instance, in the Faroese, seafood intake may be associated with low socioeconomic status, whereas in Scandinavian societies it may be associated with high socioeconomic status. If the studies are undertaken in such a way so as to enable comparison of confounder adjusted effect estimates of well-defined absolute exposure levels of seafood pollutants, consistent findings across such studies would allow stronger causal inferences. Undertaking studies in more typical European and North American settings could also have the advantage of providing results that are more generalizable and applicable to such societies. However, further studies are needed among populations with traditional marine mammal consumption to broaden the basis for their decision on whether they should change their dietary habits or not. I am aware that such studies are underway in the Faroe Islands and Greenland. Any future study should preferably be designed in such a way so as to allow a separation in time of the putative cause and effect and to allow for more efficient control for potential confounding by socioeconomic factors. Further, the use of biomarkers for intake should be supported by more direct information on dietary intake at the individual level.

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**References**


