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Exposure to organochlorines and mercury through fish and marine mammal consumption: associations with growth and duration of gestation among Inuit newborns

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Abstract

Background—Several studies have reported negative associations of polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB) and mercury (Hg) with duration of gestation and foetal growth in fish eating populations. Docosahexaenoic acid (DHA) from fish, seafood and marine mammal intake has been reported to be positively related with pregnancy duration and foetal growth. So far, it remains unclear, however, if the associations of environmental contaminants (ECs) with growth are direct or mediated through their relation with the duration of gestation and the degree to which DHA intake during pregnancy attenuates the negative association of ECs with fetal growth.

Objectives—To investigate direct and indirect associations of *in utero* exposure to ECs with foetal growth and pregnancy duration while taking into account the possible positive effects of DHA.

Methods—Pregnant Inuit women ($N = 248$) from Arctic Quebec were recruited and cord blood samples were analyzed for PCBs, HCB, Hg and DHA. Anthropometric measurements were assessed at birth. Path models were used to evaluate direct and indirect associations.

Results—Cord concentrations of PCB 153, HCB and Hg were significantly associated with shorter duration of pregnancy (β varying from -0.17 to -0.20 , $p < 0.05$). Path models indicated that the associations of PCBs, HCB and Hg with reduced foetal growth (β varying from -0.09 to -0.13 , $p < 0.05$) were mediated through their relations with shorter gestation duration. Cord DHA was indirectly related to greater growth parameters (β varying from 0.17 to 0.20 , $p < 0.05$) through its positive association with gestation duration.

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Ethics:

The participation of human subjects did occur after informed consent was obtained. The research procedures were approved by the human subjects committees of Laval University and Wayne State University.

Conclusion—Prenatal exposure to ECs was associated with reduced gestation duration, which is a recognized determinant of foetal growth. DHA intake during pregnancy appeared to have independent positive association with foetal growth by prolonging gestation. Whether these associations are causal remains to be elucidated.

Keywords

Gestation; growth; mercury; organochlorines; polyunsaturated fatty acids; prenatal exposure

1. Introduction

Benefits and risks associated with consumption of fish, seafood and marine mammals is a public health issue of great relevance for many populations around the world. These food sources often contain environmental contaminants (ECs) that cross the placenta, thereby exposing the embryo and the foetus during conception and prenatal development, periods of well-documented vulnerability to exogenous chemicals. On the other hand, fish, seafood and marine mammals are good sources of nutrients, such as n-3 polyunsaturated fatty acids (n-3 PUFAs), for which there is increasing evidence of positive effects on foetal growth and length of gestation in term infants (Makrides et al., 2006; Olsen et al., 1986; Szajewska et al., 2006).

ECs of concern for pregnant women and women of childbearing age that are consuming fish, seafood and marine mammals include methylmercury (MeHg) and organochlorine chemicals (OCs), such as polychlorinated biphenyls (PCBs) and hexachlorobenzene (HCB). OCs are a family of persistent hydrocarbon compounds used extensively in North American and European industry and agriculture from 1930 through the mid-1980's. Due to their high lipophilicity and resistance to biodegradation, OCs bioaccumulate in fatty tissues of organisms and are biomagnified through the food chain (Dewailly et al., 1993a) In the aquatic environment, mercury (Hg), which comes from both natural and anthropogenic sources, is transformed by bacteria into methylmercury (MeHg) and accumulates in seafood.

Relationships between prenatal exposure to background levels of OCs and MeHg with foetal growth and duration of gestation have been studied in several prospective and retrospective cohort studies of fish eating populations. To date, ten PCB studies have been conducted with frequent consumers of fish and/or marine mammals (Bjerregaard and Hansen, 2000; Dewailly et al., 1993b; Fein et al., 1984; Grandjean et al., 2001; Karmaus and Zhu, 2004; Murphy et al., 2010; Rylander et al., 1998; Vartiainen et al., 1998; Weisskopf et al., 2005; Wojtyniak et al., 2010). PCB exposure was associated with smaller birth weight in five of those studies (Fein et al., 1984; Karmaus and Zhu, 2004; Murphy et al., 2010; Rylander et al., 1998; Wojtyniak et al., 2010). Dewailly et al. (1993b) have found shorter body length among boys, without association with head circumference. However, smaller head circumference was observed in Fein et al. (1984) study. Shorter gestation was found to be related to cord PCB concentrations in one study (Fein et al., 1984), but not with maternal preconceptional PCBs concentrations in the New York anglers study (Murphy et al., 2010). The association of *in utero* exposure to HCB with foetal growth was reported only in one fish eating cohort (Dewailly et al., 1993b), where this OC was related to shorter body length.

Six studies in fish-eating populations have focused on *in utero* Hg exposure relationships with birth weight (Bjerregaard and Hansen, 2000; Drouillet-Pinard et al., 2010; Foldspang and Hansen, 1990; Lee et al., 2010; Mendez et al., 2010; Ramon et al., 2009), two on body length (Drouillet-Pinard et al., 2010; Ramon et al., 2009), one on head circumference (Drouillet-Pinard et al., 2010) and four on gestation duration (Bjerregaard and Hansen, 2000; Drouillet-Pinard et al., 2010; Foldspang and Hansen, 1990; Xue et al., 2007).

Significant associations were reported with smaller birth weight in four studies, and with reduced birth length in one of the Spanish cohorts (Ramon et al., 2009). Newborn head circumference was not related to maternal Hg levels in hair among French pregnant women (Drouillet-Pinard et al., 2010). In the Pregnancy Outcome and Community Health (POUCH) study, increasing risk of preterm delivery was reported among women with hair Hg concentrations above the 90th percentile (Xue et al., 2007), while the other studies did not evaluate or find a relation between Hg exposure and pregnancy duration.

Several randomized controlled trials have documented benefits of prenatal n-3 PUFAs, particularly docosahexaenoic acid (DHA), on gestation duration, reduced risk of preterm deliveries (Olsen et al., 2000) and in some instances foetal growth (Campoy et al., 2012; Helland et al., 2001; Olsen et al., 1992). Although the hypothesis that the adverse reproductive effects of OCs and MeHg might be attenuated by a high maternal intake of n-3 PUFAs was formulated two decades ago, it has received little direct scientific scrutiny. The vast majority of cohort studies conducted to date have focused either on ECs or n-3 PUFAs and did not obtain biomarkers of both. Moreover, in observational studies, a failure to control for prenatal n-3 PUFAs could lead to an underestimation of the toxicity of ECs on the outcomes of interest (Choi et al., 2008; Davidson et al., 2008).

We conducted a prospective longitudinal study to examine the potential associations of pre- and postnatal exposure to moderately high levels of OCs and Hg on duration of gestation, physical growth as well as cognitive and behavioral development in a sample of Inuit infants in Northern Quebec, Canada (Jacobson et al., 2008; Muckle et al., 2001). This paper focuses specifically on the associations of prenatal exposure to OCs and Hg with foetal growth and duration of pregnancy and addresses two research questions: If EC concentrations are negatively associated with growth parameters, are the associations direct or mediated through shortened duration of gestation? Are n-3 PUFA levels positively related to gestation duration and foetal growth, and if so, do they mitigate the potential negative effects of ECs on gestation duration and growth?

2. Materials and Methods

2.1 Population

Pregnant Inuit women from the Arctic Quebec region known as Nunavik were invited to participate in a study focusing on infant health and development. Nunavik is a region located north of the 55th parallel, in which 10 000 Inuit live in 14 villages scattered along a 2000-km coastline on the Hudson Bay, Hudson Strait, and Ungava Bay. Participants were recruited from the three largest communities on the Hudson Bay coast.

2.2 Procedures and Variables

From November 1995 to November 2001 pregnant women in these communities were invited to participate in the study at their first prenatal visit to the village nursing station. The recruitment procedure has previously been described (Muckle et al., 2001). A detailed informed consent was obtained from each participating mother. The research procedures were approved by the human subjects committees of Laval University and Wayne State University. Maternal interviews were conducted in the community's nursing station at mid-pregnancy and at 1-month postpartum by trained research assistants to assess the mothers' socioeconomic and personal characteristics. Among the 417 Nunavik women invited to participate in this study, 47 were excluded because a newborn from the same mother had been previously recruited, 9 could not be contacted by our research assistants to schedule the prenatal interview, and 110 refused to participate. Among the 251 women interviewed prenatally, 3 were subsequently excluded due to miscarriage or perinatal or postnatal

mortality. Overall, the participation rate for the study was 69%, for a total of 248 pregnant women and their newborns for whom we have information regarding environmental exposure and/or growth parameters.

2.3 Biomarkers and laboratory procedures

A 30-ml blood sample was drawn from the umbilical cord after it was severed. Concentration of the 14 most prevalent PCB congeners (IUPAC nos. 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187) and HCB, were measured in cord plasma samples. The detection limit was 0.02 µg/L for all compounds. Hg concentrations were determined in cord whole blood, as well as in the maternal hair sample collected postnatally, which was cut into three segments of 3 cm, each corresponding to a trimester of pregnancy. The detection limits were 1.0 nmol/L and 1.0 nmol/g for blood and hair Hg analysis, respectively. Fatty acids including n-3 PUFAs and DHA were determined in cord plasma phospholipids and expressed as percentages of all fatty acids from C14:0 to C24:1 (% weight). Total cholesterol, free cholesterol, triglycerides, and phospholipids in plasma were also determined. Concentrations of total plasma lipids were estimated according to the formula developed by Akins et al. (1989). Detailed laboratory procedures for ECs, n-3 PUFAs and lipids quantification and quality control data have been described previously (Jacobson et al., 2008; Muckle et al., 2001).

2.4 Outcomes

Weight, length, and head circumference at birth were measured by a midwife or nurse, who had been trained by the investigators to follow a standard protocol. Two measurements were performed for each growth parameter, and a third one was performed when a discrepancy of more than 5 g for birth weight and 0.3 cm for length and head circumference was noted. Final growth parameters were based on the average of the two closest measurements. Because determination of gestational age by ultrasound was not available for the majority of participants, duration of pregnancy was based primarily on the Ballard Examination for Foetal Maturity ($N=192$) (Ballard et al., 1991). This instrument estimates gestation duration by assessing physical and neuromuscular maturity. When the Ballard examination data were not available, duration of gestation was based on results of the ultrasound performed before 15 weeks of pregnancy ($N=10$) or if missing, on the date of the last menstrual period and a medical exam performed by a midwife at the first prenatal visit ($N=28$).

2.5 Statistical analyses

2.5.1 Control variables—Pre- and postnatal maternal interviews were conducted to assess potential confounding variables pertaining to demographic background, pregnancy history, and foetal exposure to other toxicants, such as nicotine and alcohol. Maternal height was measured by our research assistants; maternal pre-pregnancy weight was obtained from medical charts or, when missing, from maternal recall at prenatal interview. An initial screening of potential confounding variables was performed by assessing the bivariate correlation of each control variable with each outcome measure. Control variables tested were maternal age, weight, parity, maternal tobacco (number of cigarettes/day) and alcohol consumption (average absolute alcohol per day during pregnancy), socioeconomic status, sex of the baby, and cord blood lead concentrations. Covariates were initially retained as potential confounders if they were correlated with outcomes at $p < 0.20$.

2.5.2 Model testing—Cord blood concentrations of ECs were log-transformed to reduce skewness. Relationships between growth measurements and PCB 153, Hg, and HCB were examined. Multiple regression models were used to test direct associations of PCB 153,

HCB, and Hg on weight, length, head circumference and duration of pregnancy. Because duration of pregnancy may be in the causal pathway between contaminant levels and growth outcomes, this variable was considered as an outcome and was not adjusted for in the multiple linear models of growth parameters. Each potential confounder was entered individually in the linear model for each outcome to which it was related, starting with the potential confounder with the strongest association, and retained if its inclusion modified the β associated with the contaminant by at least 10%. Sex of the baby was included as an obligatory confounder in all predictive models of birth outcomes. Control variables retained in each final model are presented in footnotes of Table 3. Path models were used to test indirect associations of ECs and DHA on growth parameters through their relationship with pregnancy duration. They estimate simultaneously a series of regressions with multiple dependant variables (Kline, 2010). The path model tested in this study is shown in Figure 1. Confounding variables included in path models were the same as those retained in multiple regression models. A bilateral p -value < 0.05 was considered statistically significant. Models were tested with the statistical package Mplus 5.21.

2.5.3 Missing Data—The proportion of missing data for the predictive and outcome variables ranged from 0 – 56.5%. The highest number of missing data was observed for the biomarkers of ECs and DHA because cord blood samples were not available from 138 newborns. Although the proportion of missing cord blood data was high, there was no reason to think that the cause of missingness was related to the concentrations of ECs and DHA. Thus, the assumption that the data were missing at random (MAR) was considered reasonable even though this assumption can never be formally tested (Schafer and Graham, 2002). Assuming MAR, all models were tested with the full information maximum likelihood procedure, a state-of-the-art procedure for estimating models with missing data (Graham, 2009). Auxiliary variables can be included in these models. These variables are not predictive variables but are entered in the model because they are highly correlated with the test variables with missing data. Their role is to reduce bias in parameter estimates, including departures from the MAR assumption, and restore some of the power lost because of missing data. In the present study, the measures of contaminants and DHA obtained from maternal blood and breast milk sample analyses were used as auxiliary variables in models with missing cord values (see intercorrelations in Table 1, Supplemental Material). A series of t -tests revealed that there was no significant difference in concentrations of ECs and DHA in blood of mothers of newborns with or without available cord blood samples, except that the HCB blood level was lower for mothers of newborns for whom cord blood samples were not taken ($p = 0.02$).

3. Results

3.1 Descriptive statistics

Sociodemographic characteristics are summarized in Table 1. About 11% of women were younger than 18 years and 6% were older than 35. Only 20% of participants had completed high-school. Twenty-three percent of the participating women were primiparous, and 34% had already delivered three or more children. Most women smoked during pregnancy. Ninety-one percent of women had eaten at least one fish meal/month and 74% one marine mammal meal/month. About 15% of neonates were born before 37 weeks of gestation, and 7% weighted less than 2500 grams.

Concentrations of the 14 PCB congeners, HCB, and Hg measured in cord plasma are presented in Table 2. PCB 153 was the most prevalent congener and was highly correlated with each of the other congeners detected in at least 70% of the samples ($r = 0.87 - 0.98$). This finding supports the use of PCB 153, the most prevalent congener, as a marker of

exposure to the PCB mixture in the Arctic (Ayotte et al., 2003). HCB was detected in more than 70% of sample. Furthermore, it was less correlated with PCB 153 ($r = 0.72$) and was the only one with previously reported evidence of association with foetal growth. Cord blood Hg concentrations were moderately correlated with PCB 153 ($r = 0.28$, $p = .001$).

3.2 Direct predictive models

Because of the high intercorrelations among the ECs, their associations with each outcome were tested in separate multiple regression models. DHA was associated with ECs ($\beta = 0.29 - 0.32$, $p = 0.01$) as well as with duration of pregnancy and included in all models. Cord blood concentrations of PCB 153 and HCB were significantly associated with shorter height but not with weight and head circumference (Table 3). Cord Hg concentrations were not associated with the growth parameters. Cord concentrations of PCB 153, HCB and Hg were significantly associated with shorter duration of pregnancy.

3.3 Indirect predictive models

The degree to which the associations of the ECs and DHA on growth were mediated by their associations on pregnancy duration was tested using the path model illustrated in Figure 1 and reported in Table 4. An indirect association mediated by pregnancy duration was calculated by the product of the coefficients of the path from the EC or DHA to duration of pregnancy and the path from duration of pregnancy to the outcome, adjusted for the other variables in the model. Models were tested separately for each EC and for each outcome with cord DHA concentrations included in all models. We found significant negative indirect associations of cord concentrations of PCB 153, HCB and Hg mediated by pregnancy duration on the three growth outcomes. Removing two newborns with birth weight under 2000 grams from the models of birth weight did not change the results. Additionally, significant positive indirect associations of cord blood DHA on fetal weight, height, and head circumference mediated by pregnancy duration were observed. Specific estimates of the associations of ECs and DHA on length of gestation and the anthropometric parameters are presented in Table 2 (Supplemental Material). The predicted duration of gestation was increased by 3 days for each increase of 1% change of DHA/total fatty acids; gestation was shortened by 3 days for the difference between the first and third quartile of exposure to prenatal PCB 153 and HCB and by 8 days for that difference in exposure to prenatal Hg. Depending on the ECs, decrease of birth weight ranged from 102 to 198 g, whereas length and head circumference reduction ranged from 0.45 to 0.98 cm and 0.22 to 0.55 cm, respectively.

4. Discussion

Findings from this cohort study of Inuit newborns exposed to PCBs, organochlorine pesticides, and MeHg from environmental sources revealed that *in utero* exposure to moderately high levels of these contaminants was associated with a shortening of the period of gestation which, in turn, was associated with reduced birth weight, length and head circumference. By contrast, prenatal DHA was associated with an increase in the duration of gestation, which contributed to increased foetal growth.

In our study, cord DHA, which was positively correlated with both EC exposure and pregnancy duration, acted as a suppressor variable in the direct models. When DHA was not entered in a model, none of the contaminants were significantly associated with duration of pregnancy. In the Faroe Islands study (Grandjean et al., 2001), adjustment for DHA made the weak positive association between cord PCB concentrations and gestational length disappear, whereas in our study, inclusion of DHA in direct models revealed significant negative associations of ECs with pregnancy duration, meaning that DHA obscured the

relation between ECs and growth outcomes in observational studies. It is not clear why the inclusion of DHA in the statistical models of the two studies had not the same effects on associations. Potential explanations for this discrepancy between studies are differences in plasma concentrations of both PCBs and DHA, and in intercorrelations between those variables since fish and marine mammal species consumed in these populations are not the same. To our knowledge, no other studies have considered the potential suppressor effects of essential fatty acids from fish on the effects of ECs on foetal growth. These findings are consistent with other studies that have demonstrated negative bias from inclusion of n-3 PUFAs in analyses of effects of toxicants on neurodevelopment and cardiovascular diseases (Choi et al., 2008).

Positive association of DHA with pregnancy duration and foetal growth were also found in the indirect models. Indeed, gestational length was prolonged with increasing cord DHA concentrations, which indirectly had a significant positive effect on birth weight, length, and head circumference. Thus, increased foetal growth was apparently related to prolongation of gestation and not directly by DHA action on growth parameters. In this study, gestation duration was estimated to be 3 days longer for newborns found in the third quartile of exposure to ECs compare to the first quartile (see Supplemental Material). This fatty acid was also found to prolong the gestational period in the Faroe Islands study but did not necessarily increase foetal growth (Grandjean et al., 2001). In that study, very high levels of n-3 PUFAs actually appeared to be detrimental to birth weight. However, in our study, mean DHA concentration was 3.7%, half the level found in the Faroe Islands. Consistent with our results, meta-analyses of randomised controlled trials assessing effects of fish oil supplementation during pregnancy on obstetrical and neonatal outcomes suggest that the modest increase in birth weight and length associated with increased fish oil in the diet is mediated by the prolongation of gestation (Makrides et al., 2011). It has been suggested that reduction of prostaglandin E2 and F2 α by fatty acids could be the mechanism leading to delay in cervical ripening and initiation of labor (McGregor et al., 2001).

Prenatal exposures to PCBs and HCB in this cohort of newborns were associated with reduced birth length in the direct models. However, the indirect models revealed that these associations were actually attributable to shorter gestation duration. Two other studies, including one among Inuit participants, have also found negative associations between PCBs and pregnancy duration (Fein et al., 1984; Wojtyniak et al., 2010). Another study reported reduced birth weight among neonates born to mothers consuming contaminated fish from Lake Michigan (Karmaus and Zhu, 2004), Lake Ontario (Murphy et al., 2010) and the Baltic Sea (Rylander et al., 1998), without specifically affecting length of gestation. In fact, duration of gestation was considered as a confounder variable in most of those studies and adjusted for in multiple regression models focusing on birth weight as the main outcome. Because length of gestation could be on the causal pathway between ECs exposure and anthropometric birth outcomes, controlling for this variable can cause overadjustment bias (Schisterman et al., 2005). Absence of associations with growth parameters was also reported from the consortium study of Great Lakes sport-caught fish (Weisskopf et al., 2005), Finland (Vartiainen et al., 1998), Faroe Islands (Grandjean et al., 2001) and Greenland (Bjerregaard and Hansen, 2000).

Possible reduction of gestational length by PCBs was explored only in the New York Angler study (Murphy et al., 2010) and the first Michigan study (Fein et al., 1984). Maternal preconception PCB levels were not related to pregnancy duration in the New York Angler study, even though significant associations were observed with birth weight. On the other hand, newborns from the Michigan study with cord serum concentration above PCB detection limits were born about 9 days earlier than infants with PCB levels below the detection limit. This association is much stronger than the 3-day discrepancy found here

between the first and third quartiles of PCB exposure, but median concentration of PCB 153 in the Michigan study was 1/3 higher (120 ng/g lipids) than in our study (80 ng/g) (Longnecker et al., 2003). One possible mechanism by which PCBs can affect gestation duration is by activating the release of arachidonic acid from myometrial cells (Brant and Caruso, 2006). This fatty acid is known to induce prostaglandin secretion that contributes to cervical softening and effacement, as well as uterine contraction (Gibb, 1998).

Cord blood HCB and PCB 153 had similar associations with pregnancy duration. Although HCB was less strongly correlated with PCB congener than the other OCs, the correlation was still quite high. Consequently the HCB pregnancy duration association might be entirely or partly attributable to PCB congeners or other OCs. A negative association between maternal blood HCB concentration and gestation length was also reported among Mexican immigrants from the CHAMACOS study in California, who were exposed at levels similar to those in our sample (Fenster et al., 2006). Associations of cord HCB concentrations with birth outcomes could be explained by its capacity to disrupt thyroid hormone homeostasis (van Raaij et al., 1993), a well known risk factor for preterm birth (Casey et al., 2005).

In this study, we also found a significant negative association of cord Hg levels with pregnancy duration, which is in agreement with results from the POUCH study (Xue et al., 2007), the largest birth cohort study to investigate the association of Hg with pregnancy outcomes. In that low exposure cohort, maternal hair mercury levels above the 90th percentile (0.55 µg/g) at mid-pregnancy were associated with an increase risk to deliver before 35 weeks of gestation. Although we did not investigate the association with prematurity, Hg levels were associated with a reduction of almost 8 days in gestational length on average, an association that might have resulted in an increased prematurity rate in a larger sample. A similar relationship of Hg on duration of pregnancy was also reported among Greenlanders born to mothers with a high intake of fish and marine mammals (Foldspang and Hansen, 1990). However, these results were not replicated in another larger Greenlandic study (Bjerregaard and Hansen, 1996), in a previous cohort of Nunavik Inuit newborns (Lucas et al., 2004), or in the Faroe Islands study (Grandjean et al., 2001), which had levels of exposure to Hg that were similar to our study population. Other studies among fish-eaters have observed negative associations of prenatal Hg exposure to birth weight and/or length when adjusted on gestational age (Lee et al., 2010; Ramon et al., 2009) but did not report specific associations with gestational length. Effects of Hg on pregnancy duration remain unclear, but animal studies have revealed that this metal can promote platelet aggregation and thromboxane production (Caprino et al., 1983) and cause oxidative stress and endothelial dysfunction that may increase vascular resistance and hypertension (Wiggers et al., 2008). Whether this mechanism can account for the reduced gestation length observed in this study remains to be determined, but hypertensive disorders are well known factors of prematurity (Ferrazzani et al., 2011).

Our study has a number of strengths. First, in cord blood, we quantified both contaminants (Hg and several OCs) and essential nutrient levels derived from fish, seafood and sea mammal consumption and considered them simultaneously in the statistical analysis. Also of interest is our statistical analysis using path models which enabled us to identify direct and indirect effects of ECs on pregnancy duration and anthropometric measurements at birth. The percentage of missing data on ECs and DHA concentrations is a limitation of the study, but the use of the full information maximum likelihood procedure for missing data allowed us to reduce biased estimates, compared to the “complete data” approach (Graham, 2009). Although the Ballard examination is less precise than ultrasound for determination of gestational age, it was the best alternative due to the unavailability of ultrasound evaluation for most participating women. Also, data on maternal pre-pregnancy weight were partially based on maternal recall which could have led to random measurement errors, since weight

in Inuit women is not an issue of social desirability. These measurement errors probably underestimate the associations between ECs and foetal growth. Other weaknesses of this study are the small sample size, the exclusion of women with at-risk pregnancies who do not deliver in Nunavik, and the use of a single time-point for exposure assessment, preventing us from identifying specific windows of critical vulnerability for foetal growth.

Altogether, these results indicate that n-3 PUFA content in fish, seafood and marine mammals may mask the negative association of prenatal Hg and OCs with foetal growth in observational studies and that it is crucial to consider this beneficial nutrient in statistical analyses of risk assessment of maternal fish and seafood consumption during pregnancy. Our data suggest that moderately high levels of ECs derived from fish, seafood and marine mammals can affect foetal growth by reducing pregnancy duration. On the other hand, n-3 PUFAs may mitigate these adverse effects by prolonging pregnancy duration. These findings underscore the importance of promoting consumption of fish species with low EC content and high n-3 PUFA concentrations in order to optimize foetal growth and development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DHA	Docosahexaenoic acids
ECs	Environmental contaminants
HCB	Hexachlorobenzene
Hg	Mercury
MAR	Missing at random
MeHg	Methylmercury
n-3 PUFAs	n-3 polyunsaturated fatty acids
OCs	Organochlorine compounds
Pb	Lead
PCBs	Polychlorinated biphenyls
Se	Selenium

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Highlights

- Associations of contaminants on duration of gestation and foetal growth are equivocal.
- Fatty acids from fish appear to prolong gestation and promote foetal growth.
- We evaluated their associations on gestation duration and foetal growth in Inuit newborns.
- Contaminants negatively associated with pregnancy duration, reducing foetal growth.
- Positive association of fatty acids with gestation duration, improving foetal growth.

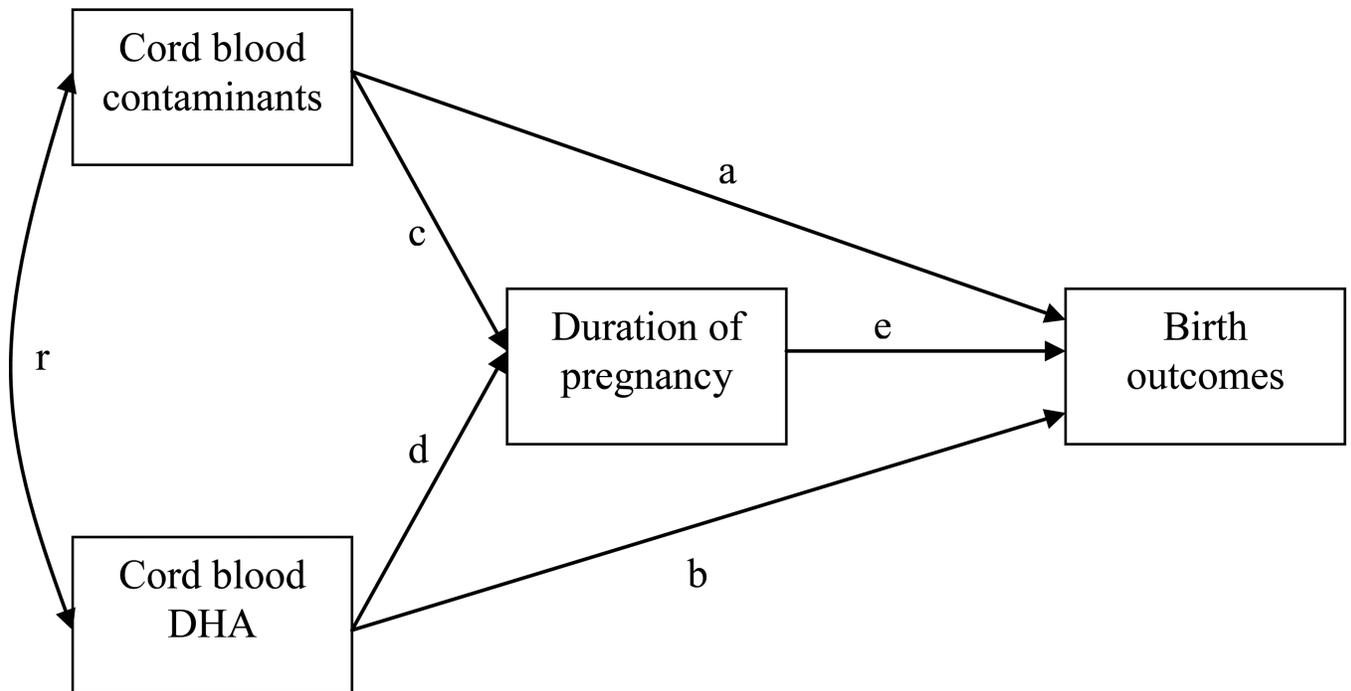


Figure 1. Representation of the indirect effects of cord blood contaminant measures and DHA

Indirect effect of contaminant on outcome = $c * e$

Indirect effect of DHA on outcome = $d * e$

Birth outcome tested are birth weight, length and head circumference; cord blood measures of contaminants tested are PCB 153, HCB and Hg

Table 1

Characteristics of participants

Characteristics	N	%	Mean	SD	Range
Maternal					
Age	248		24.9	5.8	14.1–40.7
Education (years)	248		9.0	1.7	5.5–14.3
Marital status	248				
Single		29.0			
Married		18.2			
Cohabiting not married		50.0			
Divorced, separated, widowed		2.8			
Socioeconomic status (12 months) ^a	176				
No occupation		60.8			
Unskilled labourers		6.8			
Semiskilled labourers		8.5			
Skilled craftsmen, clerical, sales		12.5			
Technical, small business		10.3			
Professionals		1.1			
Lives with parents	248	39.5			
Language of interview	248				
English		70.9			
French		16.2			
Inuktituk		12.9			
Parity	248		2.1	1.9	0–9.0
Pre-pregnancy weight (kg)	243		61.5	11.9	53.8–66.8
Pregnancy smoking (% smokers)	248	90.3			
Pregnancy smoking (# cigarettes/day)	248		9.9	6.9	0–27.5
Average absolute alcohol per day ^b	216		0.03	0.15	0–2.02
Number of fish meals/week	215		3.4	4.0	0–28.6
Number of marine mammal meals/week	215		1.5	2.4	0–23.0

Characteristics	N	%	Mean	SD	Range
Neonates					
Sex of baby (% male)	230	57.0			
Cord blood lead ($\mu\text{mol/L}$)	110		0.22	0.17	0.03–0.86
Cord blood selenium ($\mu\text{mol/L}$)	107		3.7	1.5	1.9–11.6
Cord DHA (% total phospholipids)	108		3.6	1.2	1.1–7.5
Outcomes					
Birth weight (g)	238		3427	581	1620–4800
Length (cm)	210		50.2	5.0	41.0–56.0
Head circumference (cm)	211		34.4	1.6	29.0–40.0
Duration of pregnancy (# weeks)	230		38.7	1.8	32.0–42.0

The data come from the prenatal interview unless specified otherwise. The *N* represents the total number of participants for whom data were available.

^aHollingshead Index (1975) for the mother and her partner or, if she was not self-supporting, for her primary source of support (usually her parents);

^bDuring the 2nd and 3rd trimesters of pregnancy.

Table 2

Descriptive statistics for cord plasma OC ($\mu\text{g}/\text{kg}$) and Hg ($\mu\text{g}/\text{L}$) concentrations detected in at least 70% of samples ($N = 110$)

	Percent detected	Arithmetic mean	Geometric mean	SD	Range
PCB 128	5.5				
PCB 52	22.7				
PCB 99	92.7	21.7	16.8	18.3	2.8–116.8
PCB 101	17.3				
PCB 105	12.7				
PCB 118	84.5	16.7	12.8	14.5	2.8–97.4
PCB 128	0				
PCB 138	100	70.0	53.7	56.1	9.8–313.1
PCB 153	100	113.7	84.0	95.2	12.0–550.9
PCB 156	41.8				
PCB 170	75.5	17.5	12.2	15.8	2.8–73.0
PCB 180	99.1	44.2	32.36	37.4	4.3–164.2
PCB 183	35.5				
PCB 187	92.7	20.7	16.5	14.6	3.7–84.8
Σ 14 PCB congeners ^a		343.8	273.8	258.3	70.8–1420.1
Hexachlorobenzene	100	53.3	43.9	37.9	10.6–233.6
Mercury ^b	100	21.3	16.7	15.6	2.4–97.3

 $p < 0.01$;

 $p < 0.001$.

Abbreviations: PCBs, polychlorinated biphenyls.

^aSum of all 14 congeners including congeners not detected in at least 70% of samples for which a score corresponding to half the detection limit was given;

^bHg arithmetic mean = 106.1 $\mu\text{mol}/\text{L}$.

Table 3

Association between cord concentrations of OCs and mercury and birth outcomes

	Contaminant	N	Standardized regression coefficient
Birth weight	PCB 153 ^a	248	-0.13
	Hexachlorobenzene ^b	248	-0.15
	Mercury ^c	248	-0.06
Length	PCB 153 ^d	245	-0.16 [*]
	Hexachlorobenzene ^d	245	-0.18 [*]
	Mercury ^d	245	-0.09
Head circumference	PCB 153 ^e	248	-0.01
	Hexachlorobenzene ^e	248	-0.05
	Mercury ^e	248	-0.08
Duration of pregnancy	PCB 153 ^f	230	-0.17 [*]
	Hexachlorobenzene ^f	230	-0.20 [*]
	Mercury ^f	232	-0.18 [*]

^{*} *p* 0.05

Abbreviations: PCB 153, polychlorinated biphenyl congener 153.

Confounders included in final models are:

^a maternal weight, cord DHA, absolute alcohol per day in late pregnancy, parity, socioeconomic status, sex of baby;

^b maternal pre-pregnancy weight, cord DHA, absolute alcohol per day in late pregnancy, socioeconomic status, sex;

^c cord DHA, absolute alcohol per day in late pregnancy, parity, sex;

^d maternal weight, cord DHA, sex;

^e maternal weight, parity, absolute alcohol per day in late pregnancy, cord DHA, sex;

^f cord DHA.

Table 4

Indirect associations of OCs, mercury and DHA on foetal growth mediated by duration of pregnancy^a

	N	Models	Standardized regression coefficients for effects of contaminants on outcome		Standardized regression coefficients for effects of DHA on outcome	
			Direct	Indirect	Direct	Indirect
Birth weight	248	PCB 153 / DHA	0.00	-0.13**	-0.01	0.18**
		HCB / DHA	-0.01	-0.13*	0.04	0.20**
Length	245	Mercury / DHA	0.07	-0.12*	-0.04	0.20**
		PCB 153 / DHA	-0.05	-0.10*	0.04	0.15**
		HCB / DHA	-0.06	-0.10*	0.06	0.17**
		Mercury / DHA	-0.01	-0.10*	0.05	0.17*
Head circumference	248	PCB 153 / DHA	0.09	-0.09*	-0.08	0.15**
		HCB / DHA	0.06	-0.09*	-0.06	0.14**
		Mercury / DHA	0.02	-0.10*	-0.09	0.16**

* $p < 0.05$,

** $p < 0.01$.

Abbreviations: DHA, docosahexaenoic acids; HCB, hexachlorobenzene; PCB 153, polychlorinated biphenyl congener 153.

^aConfounders are the same as those included in the models reported in Table 4.