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SHORT COMMUNICATION

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Miscarriages and stillbirths in women with a high intake of fish contaminated with persistent organochlorine compounds

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Abstract ***Objectives:*** The purpose of the present study was to assess the effect, on miscarriages and stillbirths, of persistent organochlorine compounds (POC) through dietary intake of fatty fish from the Baltic Sea. ***Methods:*** Information on miscarriages and stillbirths was collected retrospectively by a self-administered questionnaire in a cohort of fishermen's wives from the Swedish east coast (by the Baltic Sea) and in a referent cohort of west coast fishermen's wives. Current fish consumption was used as a proxy for exposure within the east coast cohort. ***Results:*** No increase in miscarriages or stillbirths was found in the east coast cohort compared with the west coast group, in fact a decrease in early miscarriages was found (OR 0.48 [95% CI 0.26–0.92]). Moreover, no increase in risk was found for current high consumers of fatty fish within the east coast cohort. ***Conclusions:*** The present data provided no evidence that dietary POC exposure increases miscarriage and stillbirth rates.

Key words Polychlorinated biphenyls · Polychlorinated dibenzofurans · Polychlorinated dibenzo-p-dioxins · Miscarriage · Stillbirth

Introduction

One of the main sources of exposure to persistent organochlorine compounds (POC), such as polychlorinated (PCDF) biphenyls (PCB), dibenzo-dioxins (PCDD) and -furans (PCDF), and dichlorodiphenyltrichloroethane (DDT), for the Swedish general population is fatty fish from the Baltic Sea [3, 28].

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In a previous study we found that wives of Swedish fishermen eat on average more than twice as much fish as subjects from the general population [24]. A cohort of fishermen's wives from the Swedish east coast (Baltic Sea) has therefore been used to study the effect on reproductive outcome, of a high dietary intake of POC-contaminated fatty fish [4, 21–24]. For comparison, a similar group from the Swedish west coast (Skagerrak and Kattegatt), where the contamination of fish is considerably less [6], was used.

Exposure to a dietary level of 5 ppm of the commercial PCB mixture Aroclor 1254 caused stillbirths in Rhesus monkeys [2]. This is about five times the dose of Aroclor 1016 needed to reduce the birth weight of the offspring of this species [5]. Rats and mice seem to be less sensitive with respect to these reproductive outcomes [11]. In humans, PCB has been found to be easily transferred across the placenta [14]. Furthermore, women hospitalized for miscarriages had higher PCB blood levels than full-term pregnancy controls [16]. However, studies on reproductive outcome among women with a high dietary intake of PCB-contaminated fish from the Great Lakes have failed to show any relationship between fish consumption and miscarriage [9, 17]. The aim of this study is to investigate whether a high dietary intake of fatty fish from the Baltic Sea leads to an increased risk of miscarriages and stillbirths.

Materials and methods

Study cohorts

This work is part of a larger study on reproductive outcome among women with a high intake of Baltic Sea fish contaminated with POC, and more detailed information is given elsewhere [4]. Briefly self-administered questionnaires, designed to study time to pregnancy (TTP), were sent to 795 and 1,851 fishermen's wives from the Swedish east and west coasts, respectively. Among the 505 (64%) east and 1,090 (59%) west coast responders, information on pregnancy outcome for the first planned pregnancy (see below) was

available for 443 and 991 subjects, respectively. Among pregnancies ending in an early miscarriage, only confirmed pregnancies were included in the analysis, thereby excluding 11 pregnancies (east, $n = 4$; west, $n = 7$).

Outcome variables

In order to avoid interference from correlation between outcomes of succeeding pregnancies, we allowed each woman to contribute with information of only her first planned pregnancy. Data on the outcome were collected, and if the pregnancy ended in a miscarriage or a stillborn infant, the gestation week was noted. Pregnancies ending in a miscarriage were included in the analysis only if they were confirmed by a home pregnancy test, or by a physician or midwife.

Exposure variables and potential confounders

As a primary exposure variable, cohort affiliation was used. Moreover, current fish consumption was used as an exposure variable within the east coast group. We had previously, for the east coast subjects, used growing up in a fishing village as a proxy measure for high consumption of fatty fish from the Baltic Sea during childhood and adolescence [4, 24]. In the current study it was not feasible to use this variable, since none of the first planned pregnancies among women who had grown up in a fishing village ended in a miscarriage or stillbirth.

In the questionnaire, current consumption of fatty fish from the Baltic Sea was assessed as 0, 1–4, 5–14 or >14 meals per month for lunch and dinner, separately. Women with a high (at least two meals per week) fatty fish consumption ($n = 179$) were compared with women with no intake of fatty fish ($n = 73$). It should be noticed that it was not possible to classify all women according to the "high" and "no" categories defined.

The PCB congener 2,2′,4,4′,5,5′-hexachlorobiphenyl (CB-153) has been found to be a useful biomarker of POC exposure [7]. In 1995, venous blood had been drawn from a sample of the east coast cohort for analysis of CB-153 in plasma [22]. This exposure measure was available for 103 women participating in the present study.

Age [27], use of oral contraceptives (OC) [20], education [19], parity [27], smoking habits [8], coffee consumption [13], employment [26], shift work [18], heavy lifting [12], and paternal age [27] were considered as potential confounders.

Background characteristics

The questionnaire focused on life style and working habits immediately before conception. There was no difference between the cohorts with respect to year of conception (median 1977 in both cohorts) or the partner's age (median 26 years in both cohorts), and only a marginal difference in the woman's age (median 22 and 23 years in the east and west coast groups, respectively). Moreover, the differences between the two cohorts with respect to the use of OC before conception, education, frequency of shift work, lifting heavy weights, and coffee consumption were small (Table 1). Furthermore, the percentage of first-parity births was high in both groups. However, there was a higher percentage of smokers in the east coast subjects, and also a somewhat higher percentage of women not gainfully employed.

There was no marked difference between east coast women with "no" and "high" fatty fish consumption, respectively, with regard to parity, coffee consumption, employment status, shift work and education and only a marginal difference regarding the woman's and her partner's ages (data not shown). Women with no fatty fish consumption were more likely to have used OC before conception (47 vs 36%) and to have performed heavy lifting (49 vs 38%) than those with a high fatty fish consumption. Women with no intake of fatty fish, as well as their partners, were less likely to be smokers than those with a high intake.

Non-responders

Data from a previous study [23] allowed a comparison between responders and non-responders with respect to reproductive outcome variables such as ever having given birth, or ever having given birth to a low birth weight or malformed child, and with respect to smoking habits, work outside the home and daily working hours. No differences were found between responders and non-responders with respect to these variables [4].

Statistics

For comparisons of miscarriage and stillbirth rates in the two cohorts, odds ratios (OR) were calculated by logistic regression stratified on gestation time (before week 12, weeks 12–28, and after week 28). Each analysis was based on the number of pregnancies at risk at the relevant time For pregnancies ending in induced abortion (east, $n = 10$; west, $n = 26$) we had no information on the

Table 1 Life style and working habits for women from the east ($n = 438$) and west ($n = 983$) coast cohorts, with known pregnancy outcome

		East coast *n* (%)	West coast *n* (%)
Smoking habits	Non-smokers	216 (49)	626 (64)
	1–9 cigarettes/day	96 (22)	196 (20)
	10–19 cigarettes/day	107 (24)	130 (13)
	≥20 cigarettes/day	18 (4)	24 (2)
Coffee consumption	Rarely/never	57 (13)	139 (14)
	1–2 cups/day	113 (26)	303 (32)
	3–4 cups/day	174 (40)	354 (37)
	≥5 cups/day	88 (21)	164 (17)
Education	9 years compulsory schooling	139 (32)	320 (33)
	Senior high school	198 (46)	456 (47)
	University/college	96 (22)	203 (21)
Working hours	Not gainfully employed	84 (19)	133 (14)
	Part time employed	74 (17)	155 (16)
	Full time employed	277 (64)	684 (70)
Shift work		61 (15)	127 (14)
Heavy lifting		148 (37)	340 (36)
First-parity birth		354 (81)	852 (87)
Use of oral contraceptives before conception		162 (37)	359 (37)

gestation week in which the termination took place. These pregnancies were included in all strata of gestation time. An analysis excluding pregnancies that were intentionally ended was performed, but it changed the results only marginally.

When analyzing the effect of fish consumption on the miscarriage rate within the east coast cohort, we did not stratify on gestation time due to the low number of late miscarriages.

Results

Cohort affiliation

A decrease in miscarriages before week 12 was found in the east coast cohort (OR 0.48 [95% Confidence Intervals (CI), 0.26–0.92]; Table 2). For later miscarriages and stillbirths no difference was found between the two groups. Inclusion of smoking habits in a multivariate model did not markedly change the effect estimate, and smoking habits were therefore not included in the final model. Employment status changed the point estimate for late miscarriages (after week 28), and adjusted ORs are therefore presented along with the crude ORs. We point out that the other potential confounders specified in Table 1 did not differ between cohorts and were therefore not included in multivariate models.

Fish consumption

No increase in risk for miscarriages and stillbirths was found for current high consumers of fatty fish within the east coast group (10% and 6% for no and high consumers, respectively; OR 0.62 [0.23, 1.66]). In multivariate models, smoking and use of OC before conception changed the effect estimate only slightly. When adjusting for heavy lifting we estimated an OR of 0.51 (95% CI 0.19, 1.43). The potential confounders that did not differ between the two groups were not included in any of the multivariate models.

CB-153

Unfortunately, CB-153 in plasma had been analyzed in only a few of the women in the present study (miscarriage, $n = 8$ and no miscarriage, $n = 95$). Available data showed no noticeable difference in CB-153 levels between east coast women with and without miscarriages (Fig. 1; $P = 0.4$, Mann-Whitney test). Thus, there was no indication that the effect of CB-153 differed from that of fish consumption.

Table 2 Miscarriages and stillbirths in cohorts of east coast (n = 438) and west coast (n = 938) fishermen's wives compared with pregnancies under risk at the time of the miscarriage. Odds ratios (OR) with 95% confidence intervals. Adjusted for employment status

	Before week 12 n (%)	Weeks 12–28 n (%)	After week 28 n (%)
East coast	12 (3)	11 (3)	5 (1)
West coast	54 (5)	27 (3)	8 (1)
Crude OR	0.48 (0.26, 0.92)	0.89 (0.44, 1.80)	1.36 (0.44, 4.19)
Adjusted OR	0.51 (0.27, 0.96)	0.90 (0.44, 1.83)	1.58 (0.50, 5.04)

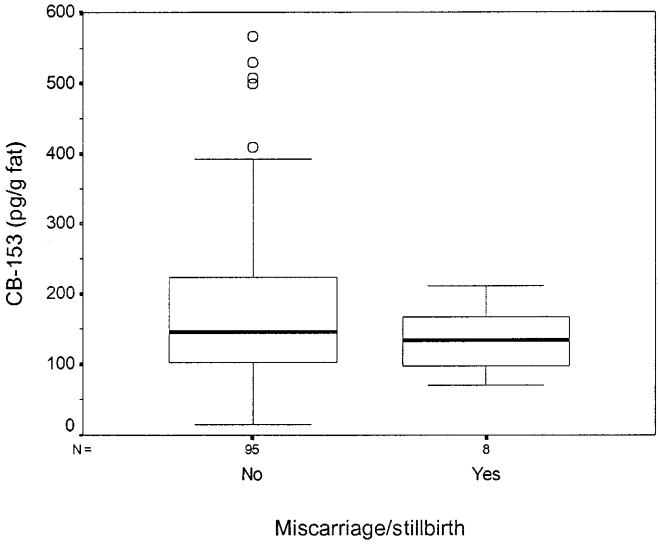

Fig. 1 Box and whiskers plot of blood levels of CB-153 for east coast cohort women with and without a miscarriage or stillbirth

Discussion

This study gave no proof of an increased risk of miscarriages or stillbirths for women with a high dietary intake of POC-contaminated fatty fish from the Baltic Sea. In fact, when considering cohort affiliation as a proxy for exposure, we found a decrease in early miscarriages. However, for late miscarriages, the results were inconclusive (reflected by a wide confidence interval) due to small numbers.

In Sweden, approximately 10% of all confirmed pregnancies end in a miscarriage [15], which is a slightly higher value than was observed for the first planned pregnancies in the present study (see Table 2). However, the proportion of miscarriages (up to week 28) increases to 8.7% among the fishermen's wives when considering each woman's first five pregnancies. The discrepancy between miscarriage rate for the first planned pregnancy and all pregnancies can be explained by the fact that women with repeated miscarriages are over-represented among those with a high parity. We can therefore conclude that there seems to be no selection bias with respect to women responding to the questionnaire.

The questionnaire used was designed to study TTP, and for some factors it was therefore focused on exposure immediately before conception. The more relevant time period is obviously early pregnancy, and some of the exposure measures employed must therefore be considered as proxies. Some of the potential confounders (coffee consumption and shift work) were not included in our analysis since they did not differ between cohorts or

fish consumption groups. Other potential confounders (smoking, heavy lifting and employment status) were included in the multivariate analysis since they did differ between groups. We have no reason to assume that cohort affiliation or fish consumption affected the proportion of women who changed life-style or work habits during early pregnancy. Thus, the effect estimate of cohort affiliation and fish consumption group would still be properly adjusted for these confounders.

We abstained from gathering data on alcohol consumption. However, we had previously found that the alcohol consumption pattern does not differ between the east and west coast cohorts [23], and therefore we find no reason to believe that the lack of information on alcohol consumption has affected the validity of our results.

The consumption of locally caught fish has been decreasing since the early 1970s [23], which suggests that the current consumption is not necessarily a good proxy for fish consumption up to early pregnancy, (the pregnancies in this study occurred between 1961 and 1997). However, we deliberately abstained from asking about fish consumption at time of conception, or before, since we have shown a low reliability of long-term recall of fish intake in these cohorts [25]. A direct measurement of body burden for POC is preferable. CB-153 in plasma is a good marker of long-term PCB exposure [7]. Unfortunately this value was available only for a minor number of the east coast cohort women, but the results from the subset of subjects with CB-153 values was well in line with the lack of association between miscarriages and stillbirths, and both cohort affiliation and consumption of fatty fish from the Baltic Sea.

The results from the present study are consistent with findings from the New York State Angler Cohort Study, where no increased risk of spontaneous fetal death was found among women with a high consumption of PCB-contaminated fish from the Lake Ontario area [17]. Similar results were also found in a study of women from Green Bay, with potential PCB exposure from Lake Michigan fish [9]. It has been shown that the estimated current dietary exposure to POC through fish consumption was comparable between groups of high consumers from the Baltic Sea and the Lake Ontario region [1]. Previous studies on high consumers of fish from the Great Lakes [10] and the Baltic Sea [22–24] have found an increased risk of giving birth to a low birth weight infant. These results agree with animal data, where a much higher dose of PCB to Rhesus monkeys was needed to induce stillbirths [2], than to result in low birth weight infants in the same species [5].

To sum up, our data showed no evidence of a negative effect on miscarriage and stillbirth frequency among women with a high dietary intake of contaminated fatty fish from the Baltic Sea.

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