

## Time to pregnancy and miscarriages in women with a high dietary intake of fish contaminated with persistent organochlorine compounds

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### Introduction

Consumption of fatty fish from the Baltic Sea, on the east coast of Sweden, is the main source of exposure for persistent organochlorine compounds (POC) for the general Swedish population (1, 2). Previous studies have shown an association between dietary intake of POC-contaminated fish and both low birthweight for infants born to exposed women (3-6) and reduction of the menstrual cycle length (7).

The main objective of this study was to assess the relationship between high dietary intake of POC-contaminated fish and decreased fertility, measured as increased time to pregnancy (TTP), and risk for miscarriage, in a cohort of fishermen's wives from the Swedish east coast. This group of women was chosen as they and their husbands have been found to eat more than twice as much fish on an average as subjects from the general population (8, 9). For relevant comparisons a similar cohort from the Swedish west coast (Skagerrak and Kattegatt), where the contamination of fish is considerably less (10), was used.

### Materials and Methods

Cohorts of women married to fishermen from the Swedish east and west coasts have been established previously (11). Women from these cohorts, born in 1945 or later, were defined as the study population. A self-administered questionnaire was sent to all women in the two cohorts, asking about background information and relevant risk factors on their five first pregnancies. The primary outcome variable, TTP, was assessed by the question "How long did it take you to get pregnant?", allowing for an open-ended answer. Each woman's first planned pregnancy was thereafter chosen for the analysis to avoid interference from correlation between TTP on succeeding pregnancies.

Data were also collected on whether the pregnancy ended in a miscarriage or a stillborn baby, and in which gestational week the pregnancy ended. For the TTP analysis, information on 399 east coast and 936 west coast pregnancies was available. The corresponding numbers in the miscarriage analysis were 443 and 992. Analyses were also performed on subfertility, defined as at some occasion having tried to get pregnant for more than 12 months without succeeding, and infertility, defined as being subfertile and never have

had being pregnant. For the analysis of subfertility there were 378 east and 819 west coast observations, and for the infertility analysis there were 407 east and 905 west coast observations. In both the subfertility and infertility analyses women who were sterile due to medical or surgical treatment were excluded.

The primary outcome variable, TTP, was analysed by using Cox regression and hereby calculating Success Rate Ratios (SuRR). For analysis of miscarriages, sub- and infertility, Odds Ratios (OR) were calculated.

## Results

In a univariate analysis of TTP an increase, although not statistically significant, in time to first planned pregnancy was found in the east coast cohort compared to the west coast cohort (SuRR 0.89, 95% CI 0.77, 1.02, table 1). Since interaction was found between cohort and smoking, with a negative correlation between the number of cigarettes smoked and SuRR, Cox regression was also performed separately for non/light smokers and heavy smokers (> 10 cigarettes/day). The results indicated that the decreased SuRR for the east coast women was present only among the heavy smokers (SuRR 0.66, 95% CI 0.49, 0.89).

Analyses were also performed adjusted for maternal age as a continuous variable, but this did not alter the results. The effects of the woman's year of birth, the partner's smoking habits, parity, and the woman's working hours were not statistically significant, neither did they change the estimate for the cohort comparison. These covariates were therefore not included in the model. The cohorts did not differ in partner's age at conception, the woman's coffee consumption, use of oral contraceptives before conception, working hours, shift work and heavy lifts. The model was therefore not adjusted for these covariates.

In the analysis of subfertility and infertility a statistically significant increase in risk was found for the east coast women (OR 2.49, 95% CI 1.05, 5.90, table 2). Even after adjusting for smoking habits the infertility ratio stayed significantly higher (OR 2.58, 95% CI 1.07, 6.22).

The analysis of miscarriage rate was performed stratified for gestational week (table 3). Each analysis was based on the number of pregnancies at risk at that time period. An increase in miscarriage rate was found for the west coast cohort for early miscarriages (OR 2.09, 95% CI 1.11, 3.95). For late miscarriages and stillbirths no differences between the two cohorts were found. Analyses were also performed adjusted for smoking habits, but this did not alter the results.

## Discussion

The results of the present study indicate an increase in TTP for women dietary exposed to contaminated fish from the Baltic Sea, and especially among women smoking more than 10 cigarettes per day. This difference between exposure effect on reproductive outcome between non/light smoking and heavy smoking women has been seen previously when heavy smokers exposed for PC was shown to have a higher OR for giving birth to a low weight child (3000 g) than did exposed non- and light smokers (3).

In the analysis of infertility, a statistically significant higher OR was found for the exposed women. In a study on Swedish midwives 3.9% of the responders reported having

tried to achieve pregnancy without success (12). Infertility of an even larger magnitude has also found in other studies on Swedish women (13, 14). This points to the possibility that there might be a low infertility frequency among the unexposed women, rather than a high one among the exposed women.

To sum up, the results of the present study indicate an association between exposure for POC and increased time to pregnancy, but not necessarily with infertility rate. Further analysis with individual exposure data needs to be done to more thoroughly investigate the effect of dietary exposure to POC on time to pregnancy.

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TABLE 1. Cox-regression models of the effect, measured as Success Rate Ratio (SuRR), of cohort on time to first planned pregnancy in an east coast vs. a west coast cohort of fishermen's wives.

All women n = 1086	Non/light smokers n = 871	Heavy smokers n = 214
SuRR (95% CI)	SuRR (95% CI)	SuRR (95% CI)
0.89 (0.77, 1.02)	0.99 (0.84, 1.16)	0.66 (0.49, 0.89)

\*Light smoker = 1-9 cig/day, Heavy smoker = 10+ cig/day

TABLE 2. Subfertility, defined as at least once having failed to achieve pregnancy within one year of trying, and infertility, defined as being subfertile and never have had being pregnant, in two cohorts of fishermen's wives. Odds Ratios (OR) comparing east coast vs. west coast women.

Cohort	Subfertility		
	All women n (%)	Non/light smokers n (%)	Heavy smokers n (%)
East Coast	88 (23)	53 (20)	33 (32)
West Coast	164 (20)	133 (19)	27 (22)
OR (95% CI)	1.21 (0.90, 1.63)		1.16 (0.86, 1.58)

Cohort	Infertility		
	All women n (%)	Non/light smokers n (%)	Heavy smokers n (%)
East Coast	11 (3)	8 (3)	3 (3)
West Coast	10 (1)	9 (1)	1 (1)
OR (95% CI)	2.49 (1.05, 5.90)	2.58 (1.07, 6.22)	

\*Light smoker = 1-9 cig/day, Heavy smoker = 10+ cig/day

TABLE 3. Miscarriages and stillbirths in two cohorts of fishermen's wives compared to pregnancies under risk at the time of the miscarriage. Odds Ratios (OR) comparing east coast vs. west coast women.

Cohort	Before week 12	Week 12-28	After week 28
East Coast	12 (3%)	11 (3%)	5 (1%)
West Coast	54 (6%)	27 (3%)	8 (1%)
OR (95% CI)	0.48 (0.25, 0.90)	0.87 (0.43, 1.78)	1.34 (0.44, 4.13)

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