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KEY WORDS
birth weight, length, head circumference, DDT, DDE, HCB, HCH, PCB

ABBREVIATIONS
OC—organochlorine compound
DDT—dichlorodiphenyltrichloroethane
DDE—1,1-dichloro-2,2-bis(*p*-dichlorodiphenyl)ethylene
HCB—hexachlorobenzene
HCH—hexachlorocyclohexane
PCB—polychlorinated biphenyl
T-Hg—total mercury
FFQ—food frequency questionnaire

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WHAT'S KNOWN ON THIS SUBJECT: There is growing concern that chemical agents could impair the anthropometric development of the fetus. However, epidemiological studies have reported inconsistent results.

WHAT THIS STUDY ADDS: The results of this study reveal that moderate prenatal exposure to some organochlorine pesticides, including 4,4′-dichlorodiphenyltrichloroethane, 4,4′-1,1-dichloro-2,2-bis(*p*-dichlorodiphenyl)ethylene, hexachlorobenzene, and β-hexachlorocyclohexane, may exert adverse health effects on birth size, reducing the birth weight, length, and head circumference.

abstract

OBJECTIVE: To investigate the possible association between birth size and cord concentrations of some organochlorine compounds (OCs), including 4,4′-dichlorodiphenyltrichloroethane (DDT), 4,4′-1,1-dichloro-2,2-bis(*p*-dichlorodiphenyl)ethylene (DDE), hexachlorobenzene (HCB), β-hexachlorocyclohexane (β-HCH), 4 polychlorinated biphenyl (PCB) congeners (118, 138, 153, and 180), and their sum (ΣPCBs) in a birth cohort in Valencia, Spain.

STUDY DESIGN: A total of 494 mothers and their newborns (born 2003–2006) participated in the study. Multivariate linear regression analyses were performed between birth weight, length, or head circumference and OC concentrations.

RESULTS: Median concentrations of 4,4′-DDT, 4,4′-DDE, HCB, β-HCH, and ΣPCBs were 0.02, 0.46, 0.22, 0.09, and 0.35 ng/mL, respectively. For birth weight there was a significant decrease of 63 and 107 g for each 10-fold increase in cord serum 4,4′-DDT and 4,4′-DDE concentrations, and a marginally significant decrease of 79 and 53 g for each 10-fold increase in HCB and β-HCH concentrations. A significant decrease of 0.39 cm in birth length was found for each 10-fold increase in HCB concentrations. For newborns with cord 4,4′-DDT concentrations above the median there was a significant decrease of 0.26 cm in birth head circumference.

CONCLUSIONS: These results reveal that prenatal exposure to some OCs could impair the anthropometric development of the fetus, reducing the birth weight, length, and head circumference. *Pediatrics* 2011; 128:e127–e134

Anthropometric development of the fetus influences perinatal, infant, and even adult health. Thus, reduced birth size has been associated with poor cognitive and neurologic development[1] and with an increased risk of chronic diseases later in life.[2]

A wide range of factors have been studied as possible contributors to adverse anthropometric development, including parental anthropometric variables, socioeconomic status, prenatal smoking, and diet.[3] There is also growing evidence that chemical agents, including some organochlorine compounds (OCs) found in human tissues and fluids,[4,5] may also be associated with adverse pregnancy outcomes.[6] Some authors related fetal growth retardation and reduced anthropometric measurements at birth to exposure to OCs,[7–9] although others found no such association.[10–12] The currently available epidemiologic evidence is therefore inadequate, and calls have been made for additional studies to elucidate the relationship between OC exposure and adverse health effects.[6]

The aim of the present study was to assess the association between birth size and prenatal exposure to some OCs, including 4 organochlorine pesticides (4,4′-dichlorodiphenyltrichloroethane [DDT]; 4,4′-1,1-dichloro-2,2-bis(*p*-dichlorodiphenyl) ethylene [DDE]; hexachlorobenzene [HCB]; and β-hexachlorocyclohexane [HCH]) and 4 polychlorinated biphenyl (PCB) congeners in a general population mother-infant cohort in Valencia, Spain. The cohort is part of the INMA (Spanish Children's Health and Environment) study, a prospective multicenter pregnancy and birth cohort study in the general Spanish population.

MATERIALS AND METHODS

Study Design and Population

Study protocols were reported previously in detail.[5,13] Briefly, the inclusion criteria were age ≥16 years, singleton pregnancy, enrollment at 10 to 13 weeks of gestation, no assisted conception, delivery scheduled at the reference hospital, and no communication handicap. The hospital ethics committee of La Fe Hospital (Valencia) approved the research protocol, and all mothers gave written informed consent before inclusion at the first trimester of pregnancy. Of the 855 women enrolled, 787 were followed to delivery (28 withdrew, 5 were lost to follow-up, 31 had induced or spontaneous abortion, and there were 4 fetal deaths). From these 787 newborns, 499 cord serum samples were available for OC determinations and 554 cord blood samples for total mercury (T-Hg) measurements. OC and T-Hg determinations were both available for a final study sample of 494 newborns. Deliveries took place between May 2004 and February 2006.

Birth Outcome Assessment

Outcome variables were birth weight (g), length (cm), and head circumference (cm). Neonates were weighed at birth by the midwife in the delivery room, and the birth length and head circumference were measured within the first 12 hours of life by a nurse in the hospital ward. Gestational age was estimated according to the date of the last menstrual period reported at recruitment or by using an early ultrasound based-gestational age of the crown-rump length when the difference between this and the self-reported last menstrual period was ≥7 days (11.9% of cases). Birth outcomes were standardized for gestational age using the residual method. Briefly, adjusted birth weight, length, and head circumference were derived by linear regression of each birth outcome against gender and gestational age. The residual value was then added to the estimated mean birth anthropometric measurement at 40 weeks to correct individual measurements to 40 weeks of gestation.[14]

Laboratory Assays

Residues of 4,4′-DDT, 2,4′-DDT, and their metabolites 4,4′-DDE, 2,4′-DDE, 4,4′-DDD, 2,4′-DDD, HCB, pentachlorobenzene, α-HCH, β-HCH, γ-HCH, and δ-HCH, and 7 individual PCB congeners (International Union of Pure and Applied Chemistry numbers 28, 52, 101, 118, 138, 153, and 180) were analyzed in umbilical cord serum. The laboratory analytical methods and quality control procedures are described elsewhere.[4,15] Briefly, OC concentrations were determined by gas chromatography with electron capture detection using an Agilent 6890N gas chromatograph with a micro-electron capture detector (Agilent Technologies, Palo Alto, CA). Percent recoveries ranged from 70% to 130% and limits of detections from 0.002 to 0.07 ng/mL. Finally, we determined total cholesterol and triglycerides by means of enzymatic techniques, calculating total serum lipid concentrations.[16]

Other Covariates

The pregnant women completed 2 detailed in-person questionnaires (weeks 10–13 and 28–32) on anthropometric and sociodemographic characteristics and lifestyle variables. Covariates considered for inclusion in the models were as follows: maternal variables (ie, age, height, pregnancy weight gain, prepregnancy BMI, country of origin, residence, parity, education, employment during pregnancy, socioeconomic status [according to current or most recent occupation, and in the case of full-time housewives, according to the husband's occupation], cohabitation with the infant's father, and consumption of tobacco [smoking at least 1 cigarette per day during the third trimester]); paternal variables (ie, height and BMI); the in-

fant's gender; and T-Hg concentrations (in quartiles) in cord blood because this contaminant was previously associated with adverse anthropometric measurements in the same cohort.[13]

As described previously,[13] a semiquantitative food frequency questionnaire (FFQ) was used to assess the usual daily dietary intake during pregnancy in 2 different interviews: the first collected information since the last menstrual period to the end of the first trimester (10–13 weeks); and the second was held at 28 to 32 weeks and collected dietary information for the period since the first FFQ was administered. The 100-item FFQ is an expanded version of a previous 93-item FFQ similar to the Harvard questionnaire,[17] which we validated and developed for an adult Spanish population in Valencia with a high proportion of women.[18] Participants were asked to report the frequency of consumption of 100 foods commonly eaten in Spain, including 12 vegetable and 11 fish items. Standard units or serving sizes were specified for each food item in the FFQ, and the response to each food item was converted to average daily intake in grams for each woman. Total energy, caffeine, and alcohol intakes were primarily obtained from food composition tables of the US Department of Agriculture.[19] In our models we considered the mean dietary intake of fish, vegetables, alcohol, caffeine, and energy obtained from both FFQs.

Statistical Methods

We determined the relationships between birth outcomes and OC concentrations found in umbilical cord serum with detection frequency > 50% (4,4′-DDT; 4,4′-DDE; HCB; β-HCH; PCBs 118, 138, 153, and 180; and their sum [ΣPCBs]). OC concentrations were $\log_{10}$-transformed because OC distributions were skewed to the right. Parameter estimates of the regression models were expressed as the change in the response variable associated with a 10-fold increase in the exposure variable.

For descriptive purposes, we present percentages for categorical variables, means and SDs for continuous variables approximately normally distributed, and medians and interquartile ranges for skewed variables. Differences in study variables between the nonincluded and included populations were contrasted by using the χ^2 test, unpaired Student's t test, or Mann-Whitney test.

We performed bivariate analysis to determine covariates associated with birth outcomes by using linear regression. We also examined the relationship between OC concentrations and covariates by using simple regression analyses for ΣPCBs and 4,4′-DDE, and Tobit regression analyses for the remainder to obtain maximum likelihood estimates of the coefficients in the presence of censored values (ie, values below the limit of detection). Multivariate models were adjusted for those covariates associated with birth outcomes in bivariate analyses at a significance level of $P \leq .20$, sequentially excluding nonsignificant variables from the model after a backward procedure, using the likelihood ratio test. In these models, potential confounders for OCs were also retained if the OC coefficient changed by >10% when they were dropped. The mother's age and T-Hg concentrations were included in all models regardless of their statistical significance. To assess the shape and evaluate the linearity of the relationship between OC concentrations and birth outcomes, we used adjusted general additive models, comparing models with OC concentrations in a linear and nonlinear manner (a cubic smoothing spline with 2, 3, and 4 degrees of freedom) by means of graphical examination and likelihood ratio test. No significant improvement in the model (likelihood ratio test, $P >$ .05) was obtained with nonlinear models for continuous variables except in the case of head circumference and 4,4′-DDT or β-HCH. Therefore, we studied the association between birth size and OC concentrations as continuous variables, and in the case of head circumference and 4,4′-DDT or β-HCH as both continuous and dichotomous variables (median values as cutoff points).

OCs were examined separately, replacing values below the limit of detection with half the limit of detection value. For descriptive analyses, OC concentrations were expressed in ng/mL or were lipid-adjusted (ng/g lipid), dividing serum residue concentrations by total serum lipid concentrations. For statistical analyses, OC concentrations were expressed in ng/mL, and total serum lipid concentration was considered as a separate term in models. Lipid analysis results were missing in 24 cord serum samples and were replaced with the mean lipid value in the statistical analyses. Sensitivity analyses excluding the 24 missing lipid cases as well as excluding preterm infants were performed. Because no major differences were found, we present the results with all cases included. The normality and homoscedasticity of regression residuals also were assessed and verified.

RESULTS

Study Population

In Table 1, the characteristics are shown of the pregnant women for whom both OC and T-Hg concentrations were determined (n = 494) and for those without these data (n = 293). The mean age of the mothers with OC determinations was 30 years (range: 15–43 years). In general, characteris-

TABLE 1 Characteristics of the Study Population, INMA-Valencia Cohort, 2004–2006

Variable	Not Included ($N = 293$)	Included ($N = 494$)	P^a
Mothers			
Age, mean (SD), y	29.7 (4.3)	29.9 (4.7)	.41
Height, mean (SD), cm	162 (6.0)	162 (6.6)	.35
Weight gain, mean (SD), kg/wk	0.43 (0.17)	0.42 (0.17)	.42
Prepregnancy BMI, median (IQR), kg/m^2	22.5 (20.5–25.3)	22.8 (20.8–25.9)	.21
Country, *n* (%)			
Spain	258 (88.1)	436 (88.3)	.08
Latin America	18 (6.1)	43 (8.7)	
Other	17 (5.8)	15 (3.0)	
Residence, *n* (%)			
Urban	19 (6.5)	51 (10.3)	.01
Metropolitan	142 (48.8)	242 (49.1)	
Semiurban	102 (35.1)	181 (36.6)	
Rural	28 (9.6)	20 (4.1)	
Parity, *n* (%)			
None	161 (55.0)	272 (55.1)	.99
1	107 (36.5)	180 (36.4)	
>1	25 (8.5)	42 (8.5)	
Education, *n* (%)			
Up to primary	91 (31.1)	176 (35.6)	.33
Secondary	134 (45.7)	201 (40.7)	
University	68 (23.2)	117 (23.7)	
Employment, *n* (%)			
Employed	242 (82.6)	409 (82.6)	.94
Unemployed	51 (17.4)	85 (17.4)	
Social class, *n* (%)			
IV+V (lowest)	178 (60.8)	298 (60.3)	.83
III	72 (24.6)	116 (23.5)	
I+II (highest)	43 (14.7)	80 (16.2)	
Cohabitant, *n* (%)			
Infant's father	284 (96.9)	481 (97.4)	.72
Others	9 (3.1)	13 (2.6)	
Smoking, *n* (%)			
Yes	71 (24.5)	108 (22.0)	.43
No	219 (75.5)	382 (78.0)	
Alcohol, *n* (%)			
0 g/d	159 (54.3)	283 (57.3)	.71
0–1 g/d	102 (34.8)	161 (32.6)	
>1 g/d	32 (10.9)	50 (10.1)	
Caffeine, *n* (%)			
0–100 mg/d	216 (73.7)	379 (76.7)	.22
>100–200 mg/d	45 (15.4)	79 (16.0)	
>200 mg/d	32 (10.9)	36 (7.3)	
Fish intake, median (IQR), g/d	61.1 (41.9–86.1)	61.3 (44.1–86.2)	.99
Vegetable intake, median (IQR), g/d	206 (138–272)	199 (133–270)	.45
Fathers			
Age, mean (SD), y	31.5 (5.0)	32.0 (5.1)	.29
Height, mean (SD), cm	175 (7.4)	176 (7.1)	.59
BMI, median (IQR), kg/m^2	(23.5–27.8)	25.4 (23.7–27.8)	.44
Newborns			
Birth weight, mean (SD), g	3289 (429)	3345 (433)	.08
Birth length, mean (SD), cm	50.4 (1.8)	50.6 (1.9)	.30
Birth HC, mean (SD), cm	34.3 (1.3)	34.3 (1.3)	.40
Gender, *n* (%)			
Male	148 (50.5)	269 (54.5)	.28
Female	145 (49.5)	225 (45.6)	

IQR indicates interquartile range; HC, head circumference.

[a] From χ^2-test, Student's *t* test, or Mann-Whitney test.

tics of the included population were comparable to those of the nonincluded group (without OC data), except that the latter contained a significantly higher proportion of mothers with rural residence (Table 1).

OC Concentrations in Umbilical Cord Serum

In Table 2, the geometric mean; 95% confidence interval; and 25, 50, 75, and 95 percentiles of OC concentrations in umbilical cord serum ($n = 494$) are shown, expressed in ng/mL. Briefly, median 4,4′-DDE and ΣPCB values were 0.46 and 0.35 ng/mL, respectively. Mean total lipid content (n = 475) of cord serum was 256(56) mg/dL. Median 4,4′-DDT, 4,4′-DDE, HCB, and β-HCH values were 8.3, 189, 87, and 35 ng/g lipid, respectively; and median PCB 118, 138, 153, 180, and ΣPCB values were 23, 34, 46, 34, and 294 ng/g lipid, respectively.

Cord OC Concentrations and Fetal Growth Outcomes

In Table 3, the adjusted regression analyses are shown for the relationship of birth weight, length, and head circumference with $\log_{10}$-transformed cord serum OC concentrations. Birth weight showed a significant inverse association with 4,4′-DDT ($\beta = -63$; $P = .022$) and 4,4′-DDE ($\beta = -107$; $P = .038$) concentrations and a marginally significant inverse association with HCB ($\beta = -79$; $P = .081$) and β-HCH ($\beta = -53$; $P = .057$) concentrations. Birth length showed a significant negative association with HCB ($\beta = -0.39$; $P = .047$) concentrations, and this association was marginally significant in the case of PCB 153 ($\beta = -0.46$; $P = .093$). When exposure to 4,4′-DDT was analyzed as a dichotomous variable, a significantly lower head circumference was found in newborns with concentrations above the median ($\beta = -0.26$ [95% confidence interval: −0.48 to −0.03]; $P = .028$).

DISCUSSION

The results of this study of a cohort from Valencia reveal that prenatal exposure to OCs may exert adverse health effects on birth size, reducing

TABLE 2 Concentrations of OCs ($N = 494$) in Umbilical Cord Serum in INMA-Valencia Cohort, 2004–2006

OCs[a]	LOD, %	>LOD, %	GM	95% CI	25th Percentile	50th Percentile	75th Percentile	95th Percentile
4,4′-DDT	0.009	54.7	0.020	0.017–0.023	<LOD	0.020	0.074	0.230
4,4′-DDE	0.016	99.8	0.495	0.458–0.535	0.296	0.464	0.770	1.824
HCB	0.035	92.1	0.188	0.172–0.206	0.127	0.222	0.363	0.707
β-HCH	0.008	78.1	0.050	0.044–0.058	0.018	0.085	0.150	0.349
PCB 118	0.029	72.5	0.049	0.045–0.054	<LOD	0.062	0.102	0.217
PCB 138	0.031	86.0	0.071	0.066–0.077	LOD	0.085	0.119	0.223
PCB 153	0.020	94.7	0.100	0.093–0.107	0.079	0.113	0.158	0.261
PCB 180	0.018	91.7	0.069	0.064–0.074	0.050	0.082	0.114	0.188
ΣPCBs[b]	—	—	0.327	0.308–0.346	0.235	0.354	0.501	0.781

LOD indicates limit of detection; GM, geometric mean; CI, confidence interval.

[a] Concentrations expressed in ng/mL.

[b] Sum of 4 PCBs (118, 138, 153, 180).

TABLE 3 Effects of OC Concentrations in Umbilical Cord Serum ($N = 494$) on Birth Outcomes, INMA-Valencia Cohort, 2004–2006

OCs	Birth Weight[a]			Birth Length[b]			Birth Head Circumference[c]		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
4,4′-DDT	−63.04	−116.91–−9.17	.022	−0.06	−0.31–0.18	.602	−0.11	−0.28–0.06	.222
4,4′-DDE	−107.39	−208.88–−5.91	.038	−0.13	−0.58–0.32	.579	0.04	−0.28–0.35	.822
HCB	−79.40	−168.48–9.69	.081	−0.39	−0.77–−0.01	.047	0.07	−0.21–0.35	.605
β-HCH	−53.13	−107.80–1.53	.057	−0.09	−0.34–0.15	.457	−0.03	−0.21–0.15	.739
PCB 118	46.92	−37.50–131.34	.275	−0.10	−0.49–0.28	.591	0.15	−0.12–0.42	.282
PCB 138	−8.36	−115.39–98.67	.878	−0.18	−0.64–0.28	.437	0.11	−0.22–0.44	.519
PCB 153	−67.00	−194.62–60.63	.303	−0.46	−1.00–0.08	.093	−0.14	−0.53–0.25	.471
PCB 180	−84.69	−198.12–28.74	.143	−0.32	−0.80–0.16	.193	−0.23	−0.58–0.12	.194
ΣPCBs[d]	−2.78	−64.03–58.48	.929	−0.16	−0.42–0.11	.250	0.03	−0.16–0.22	.762

OCs were $\log_{10}$-transformed before analysis, and the coefficients were interpreted as the change in birth outcomes associated with a 10-fold increase in exposure variable. All models were adjusted by maternal age and height, smoking in third trimester, T-Hg in quartiles in cord blood, and lipid content of cord serum. CI indicates confidence interval.

[a] Adjusted for maternal variables: prepregnancy BMI; weight gain during pregnancy; country of origin; parity; fish, vegetable, and energy intakes during pregnancy; paternal height and BMI; and gender of newborn.

[b] Adjusted for maternal variables: BMI, weight gain during pregnancy, social class, residence; paternal BMI; gender of newborn.

[c] Adjusted for maternal variables: fish, and energy intakes during pregnancy.

[d] Sum of 4 PCBs (PCB 118, 138, 153, 180).

the birth weight, length, and head circumference.

A significant decrease of 63 and 107 g in birth weight was found for each 10-fold increase in cord serum 4,4′-DDT and 4,4′-DDE concentrations, respectively. Newborns with cord 4,4′-DDT concentrations >0.02 ng/mL showed a significant decrease of 0.26 cm in birth head circumference. The possible associations between concentrations of 4,4′-DDT and/or 4,4′-DDE and fetal growth outcomes have been examined in several cohorts worldwide (Table 4) with conflicting results, with inverse significant associations reported by some studies[7,8,20–22] but not by others.[9–12,23–28] In a study in the United States, an increased risk of small weight for gestational age was associated with higher maternal 4,4′-DDE concentrations.[21] In India, a positive association was reported between an increased risk of fetal growth retardation in weight and maternal blood 4,4′-DDE concentrations, and an inverse association between birth weight and cord blood 4,4′-DDE concentrations.[7] In the Great Lakes area of the United States, an inverse relationship was reported between birth weight and maternal DDE blood concentrations.[8] More recently, lower head circumference (in New York)[20] and birth weight (in Poland)[22] were found to be associated with higher maternal 4,4′-DDE concentrations. In Singapore, a positive association was reported between birth weight, length or head circumference, and cord 4,4′-DDT concentrations.[29]

In the present study, we found a 0.39 cm and 79 g decrease in birth length and weight, respectively, for each 10-fold increase in HCB, although the association only reached significance in the former case. In few studies (Table 4) has the association between HCB exposure and birth size been investigated, and the results have been inconsistent. A significant decrease in length of male Inuit neonates was associated with higher breast milk HCB concentrations.[23] In Germany, an association was reported between lower birth weight in female infants and higher maternal milk HCB concentrations.[24] An association between birth length and cord HCB concentrations was found in another Spanish area.[25] In Norway, an association was reported between increased maternal milk HCB concentrations and decreased birth weight, length, and head

TABLE 4 Associations Between Birth Weight and 4,4′-DDT, 4,4′-DDE, HCB, and β-HCH Concentrations in Different Studies

Source	Collection	Country	Matrix	*N*	DDT	DDE	HCB	HCH	Concentrations[a]
Dewailly et al, 1993	1989–1990	Canada	Milk	94	—	→	→	—	NS
Schade and Heinzow, 1998	1995–1997	Germany	Milk	246	→	→	↓	↓	DDT[b], HCB, β-HCH: 202, 65, 36 ng/g lipid
Ribas-Fito et al, 2002	1997–1999	Spain	Cord serum	70	—	→	→	→	DDE, HCB, β-HCH: 0.85, 1, 0.54 ng/mL
Siddiqui et al, 2003	NS	India	Cord blood	54	→	↓	—	→	DDT, DDE, β-HCH mean:[c] 0.22, 5, 3 ng/mL
Karmaus and Zhu, 2004	1979–1991	United States	Maternal serum	168	—	→	—	—	DDE <5 ng/mL: 27.4%
Farhang et al, 2005	1959–1967	United States	Maternal serum	420	→	→	—	—	DDT, DDE: 11, 43 ng/mL
Weisskopf et al, 2005	1994–1995	United States	Maternal serum	143	—	↓	—	—	DDE range: 0.13–10 ng/mL
Fenster et al, 2006	1999–2000	United States	Maternal serum	385	→	→	→	→	OC[d]: 12, 1004, 65, 37 ng/g lipid
Khanjani and Sim, 2006	1991–1992	Australia	Milk	815	→	→	—	—	DDT, DDE < 7500 ng/g lipid
Khanjani and Sim, 2006	1991–1992	Australia	Milk	815	—	—	→	→	HCB, β-HCH: 35, <5 ng/g lipid
Lopez-Espinosa et al, 2007	2000–2002	Spain	Placenta	150	→	→	—	—	DDT, DDE: 0.5, 2 ng/g placenta
Sagiv et al, 2007	1993–1998	United States	Cord serum	722	—	→	→	—	DDE, HCB: 0.3, 0.023 ng/mL
Wolff et al, 2007	1998–2002	United States	Maternal plasma	178	—	→[e]	—	—	DDE: 0.64 ng/mL
Eggesbo et al, 2009	2003–2006	Norway	Milk	300	—	—	↓	—	HCB: 12 ng/g lipid
Tan et al, 2009	2006	Singapore	Cord blood	41	↑	—	—	→	DDT, β-HCH: 22, 3 ng/g lipid
Brucker-Davis et al, 2010	2002–2005	France	Milk	69[f]	—	→[e]	→[e]	—	DDE, HCB: 80, 23 ng/g lipid
Wojtyniak et al, 2010	2002–2004	Poland	Maternal serum	258	—	↓	—	—	DDE: 365 ng/g lipid
This study	2004–2006	Spain	Cord serum	494	↓	↓	→[e]	→[e]	OC[d]: 0.02, 0.46, 0.22, 0.09 ng/mL

NS indicates nonspecified; ↓, negative association; ↑, positive association; →, no association ($P > .05$); — indicates OC not studied.

[a] Median OC concentrations in all cases unless otherwise specified.

[b] DDT = DDT + DDE.

[c] Concentrations in normal-weight infants.

[d] OC concentrations of DDT, DDE, HCB, and β-HCH, respectively.

[e] $P < .10$.

[f] $n = 26$ in the case of HCB.

circumference, although this association was restricted to past or current smokers.[30] A significant association was recently reported in France between lower head circumference and higher cord HCB concentrations.[28] Other authors found associations in the same direction, although statistical significance was not reached.[9,12,31]

Our study population revealed a marginally significant association between a 53 g decrease in birth weight and a 10-fold increase in β-HCH. In few studies (Table 4) has the reproductive health consequences of prenatal β-HCH exposure been examined, with controversial findings. An association was reported between higher breast milk β-HCH concentrations and lower female birth weight,[24] and between higher cord β-HCH concentrations and higher birth length and head circumference,[29] but other reports showed no associations with birth outcomes.[7,12,25,31]

We found no association between anthropometric development and exposure to PCBs in the present newborn serum samples. The children of mothers exposed to accidentally high concentrations of PCBs and related compounds have shown growth retardation and decreased birth size,[32] but the effects of low-level exposure have not been established, and an association was reported by some authors,[9,26,28] but not by others.[8,20,25] PCBs represent a group of multiple individual compounds with varying concentrations of toxicity, and differences in the types and the mixtures of PCBs studied may account for the disparities in observations.

Inconsistent findings regarding OCs and fetal growth outcomes also may be explained by differences in the matrix used for exposure quantification or in the study populations. Some authors[9] have suggested that an association between adverse fetal growth outcomes and OCs can be detected only in populations with high OC exposure. The present findings do not support this proposition because the OC exposure in our cohort was moderate in comparison to other studies (Table 4).

The biological mechanisms that underlie the effects of OCs on fetal growth are not well established. The chemicals included in the present study are known to be environmental endocrine disrupters with the capacity to bind to intracellular estrogen/androgen receptors[33] and to alter levels of circulating thyroid hormones during pregnancy.[15] Thyroid hormones play an important role in somatic growth and are involved in the differentiation and functions of several target tissues during development.[34] OC-induced hormonal changes may therefore impair normal fetal development.

One limitation of our study is that complete information on OCs was not available for the entire cohort (494 vs 787), reducing the statistical power. A selection bias is also possible if the women with available OC data differed from those without these data. However, no

statistically significant differences were observed between these groups in the main study variables. An additional difficulty in this type of study is that humans are simultaneously exposed to a huge variety of chemicals, some of which are highly correlated, including the OCs studied in the present study, which could confound our results. The strengths of the study include the fact that it started in early pregnancy, allowing the collection of an extensive set of data on potential risk factors for reduced anthropometry. Moreover, we lost few participants between recruitment and the delivery. The use of cord serum to measure OC exposure is a notable strength of this study because it is perhaps the most direct measure of contaminants passed to the fetus during pregnancy. Finally, we also obtained information on T-Hg cord concentrations and were therefore able to demonstrate that our results were not confounded by prenatal exposure to this contaminant.

CONCLUSIONS

The results of this study reveal an association between prenatal exposure to some OCs and the anthropometric development of the fetus, reducing its weight, length, and head circumference. These findings are not because of extreme exposure conditions because OC concentrations in the study area were moderate in comparison to other recent reports.

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Prenatal Exposure to Organochlorine Compounds and Birth Size

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