Organochlorine Compounds and Ultrasound Measurements of Fetal Growth in the INMA Cohort (Spain)

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Introduction

Fetal growth is an important indicator of child health because its impairment may be associated with poor neurodevelopment (Richards et al. 2002) and with chronic diseases in adulthood (Barker 2007). It has been hypothesized that some organochlorine compounds (OCs) can cross the placenta (Vizcaíno et al. 2014a) and may interfere with fetal development and growth (Windham and Fenster 2008).

To date, most studies on prenatal exposure to OCs and fetal growth have used anthropometric measures at birth (El Majidi et al. 2012; Govarts et al. 2012) and, to a lesser extent, outcomes such as being small for gestational age (Ribas-Fitó et al. 2002) as proxy measures of in utero growth. A limitation with these approaches is that fetal growth can be assessed only after delivery, and they do not allow different patterns of development to be examined throughout pregnancy. Thus, growth-retarded fetuses and healthy but constitutionally small ones may have the same birth weight (Gardosi 2004). In addition, it has been suggested that birth weight poorly reflects fetal growth during the first two trimesters of pregnancy (Gardosi 2004). Finally, assessment of birth size does not fully capture the time during gestation in which fetal growth failures begin or the onset of transient effects that may occur during intrauterine life. Therefore, the study of the effects of these contaminants on fetal growth using longitudinal ultrasound measurements may be useful to identify specific prenatal periods of vulnerability to OC exposure, and especially the age at which fetal growth failure may begin.

Within the Spanish INMA (INFancia y Medio Ambiente; Childhood and Environment) Project, we aimed to examine the relationship between maternal and cord concentrations of 4,4′-dichlorodiphenyldichloroethylene (4,4′-DDE), hexachlorobenzene (HCB), and three polychlorinated biphenyls (PCBs) (congeners 138, 153, and 180) and fetal growth using serial ultrasound measurements at 12, 20, and 34 weeks of gestation as well as size at gestational week 34 for the four parameters. We studied the association between OCs and the fetal outcomes by cohort-specific linear models and subsequent meta-analyses.

Results

PCBs were associated with a reduction in AC up to mid-pregnancy, and BPD and FL from gestational week 20 onward. An inverse association was also found between HCB and AC growth in early pregnancy. The reduction of these parameters ranged from –4% to –2% for a doubling in the OC concentrations. No association between 4,4′-DDE and fetal growth was observed.

Conclusions

To our knowledge, this is the first study to report an association between prenatal exposure to some PCBs and HCB and fetal growth: AC during the first two trimesters of pregnancy, and BPD and FL later in pregnancy.

Citation: Lopez-Espinosa MJ, Murcia M, Iñiguez C, Vizcaíno E, Costa O, Fernández-Somoano A, Basterrechea M, Lertxundi A, Guxens M, Gascon M, Goñi-Irigoyen F, Grimalt JO, Tardón A, Ballester F. 2016. Organochlorine compounds and ultrasound measurements of fetal growth in the INMA cohort (Spain). Environ Health Perspect 124:157–163; http://dx.doi.org/10.1289/ehp.1408907.
committees of each region approved the research protocol.

A total of 2,644 eligible women (≥ 16 years, singleton pregnancy, enrollment at 10–13 weeks of gestation, nonassisted conception, delivery scheduled at the reference hospital, and no communication impairment) were recruited in the first trimester of pregnancy and gave their written informed consent before inclusion (2003–2008). After we excluded the women who withdrew from the study, were lost to follow-up, or had induced or spontaneous abortions or fetal deaths, 2,506 (95%) women were followed up to delivery (May 2004–August 2008). In the present study, the sample size was 2,407 pregnant women and gave their written informed consent before inclusion (2003–2008). After enrollment hospital, and no communication impairment the present study, the sample size was 2,407 pregnant women and gave their written informed consent before inclusion (2003–2008). After enrollment the present study, the sample size was 2,407 pregnant women and gave their written informed consent before inclusion (2003–2008). After enrollment

OC exposure assessment. We measured OC concentrations in maternal serum and cord serum samples of the four cohorts and in umbilical cord serum samples of three cohorts (Asturias, Gipuzkoa, and Valencia). Samples collected in Gipuzkoa and Sabadell were analyzed at the Basque Government’s Public Health Laboratory in San Sebastian (limit of detection (LOD) of 0.071 ng/mL for all the OCs), and samples from Asturias and Valencia were analyzed at the Barcelona Institute of Environmental Assessment and Water Research (LODs of OCs between 0.010

Table 1. Study population: the INMA Project, 2003–2008 (Spain) (n = 2,407).

| Variable | Mean ± SD or n(%) |
|----------|-----------------|
| Maternal characteristics | |
| Age (years) | 31 ± 4.3 |
| Height (cm) | 163 ± 6.2 |
| BMIa (kg/m²) | 24 ± 4.4 |
| Recommended GWGb | 890 (38) |
| Born in Spain | 2,209 (92) |
| Primary studies | 588 (25) |
| Working in pregnancy | 2,008 (83) |
| Lowest social class | 1,045 (43) |
| Rural residence | 141 (6) |
| Primiparous | 1,347 (56) |
| Smoking | 739 (32) |
| Passive smoking | 1,452 (62) |
| Alcohol intake | 298 (13) |
| Paternal characteristics | |
| Height (cm) | 176 ± 7.0 |
| BMI (kg/m²) | 26 ± 3.4 |
| Child characteristics | |
| Sex (male) | 1,245 (52) |

Abbreviations: BMI: body mass index; GWG: gestational weight gain.

*Prepregnancy BMI. bRecommended GWG during the 2nd and 3rd trimester according to the prepregnancy BMI: 0.44–0.58, 0.35–0.50, 0.23–0.33, and 0.17–0.27 kg/week for underweight, normal, overweight, and obese women, respectively (Rasmussen et al. 2009). *At week 12 of pregnancy.
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1.1: managerial jobs, senior technical staff, and commercial managers; class II: skilled nonmanual workers; and class III: manual workers (Domingo-Salvany et al. 2000); parity (0 and ≥ 1 births); tobacco consumption at week 12 of pregnancy (yes and no); passive smoking at home, workplace, or leisure areas/restaurants (yes and no); season of last menstrual period; and intake of vegetables (grams/day), fruit (grams/day), seafood (including three variables: lean fish, oily fish, and other seafood in grams/day); total energy (kilocalories/day); and beverages containing alcohol (yes and no). We also considered paternal height (centimeters) and BMI (kilograms per meter squared), and sex of the fetus.

Statistical analysis. For descriptive purposes, we present numbers and percentages for categorical variables, and means and SDs for continuous variables. Percentiles (P) 25, 50, and 75 are presented for OCs. We evaluated placental transfer by calculating P25, P50, and P75 of the ratios of maternal and umbilical cord OC concentrations, and Pearson partial correlations between the compounds (log2,OC) measured by cohort. We also used Pearson correlations adjusted by cohort to describe pairwise relationships between log2,OC measured in the same matrix. Contaminant concentrations are expressed as wet-weight concentrations (nanograms per milliliter) and in nanograms per gram lipid for descriptive analyses.

We conducted multiple linear regression analyses to analyze the association between maternal and cord serum OC concentrations and SDs scores of fetal growth measurements at weeks 0–12, 12–20, 20–34, and size at 34 weeks of gestation. We used wet-weight OC concentrations with adjustment for maternal or cord lipid levels as a separate term to minimize potential biases due to lipid standardization (Schisterman et al. 2005), after log2,OC transformation of OC [log2(OC)] and lipid concentrations to account for right skewed distributions. To identify predictor and confounder variables, we conducted linear regression analyses to determine covariates associated with fetal growth outcomes [excluding the fixed imputation of LOD/2 by assuming a log-normal distribution of OCs and conditioning the imputation to the range (0, LOD)]. We generated a total of 50 complete data sets by using the mice package for R (van Buuren and Groothuis-Oudshoorn 2011), and estimates on each data set were combined using Rubin’s rules for multiple imputation (Little and Rubin 2002). To impute OC values < LOD, we defined an additional function for bootstrap multiple imputation of interval censored variables (Lubin et al. 2004). Information on the multiple imputation procedure is available in the Supplemental Material, “Details on multiple imputation (MI) modeling,” and Table S2. All results in the present paper (including the description of OC concentrations, the Pearson correlation analyses, and the final cohort-specific adjusted models) were based on pooled estimates from a multiple imputed data set.

We carried out different sensitivity analyses to evaluate the robustness of the results. First, we compared models using multiple imputation (the main analysis of our study) with the complete case analysis
Results

Study population characteristics. Table 1 shows the characteristics of the study population. Mean maternal age was 31 years (range, 16–43 years); 56% of the mothers were primiparous, and 32% were smokers at the beginning of pregnancy.

OC concentrations. Wet-weight concentrations of OCs in maternal and cord serum samples are shown in Table 2. We used individual total lipid values to calculate OC concentrations on a lipid content basis. Maternal medians for 4,4'-DDE, HCB, as well as for PCBs 138, 153, and 180, were 141, 50, 29, 48, and 34 ng/g lipid, respectively. Respective cord medians were 154, 61, 141, 50, 29, 48, and 34 ng/g lipid (data not shown).

Maternal and cord serum OC correlations and placental transfer of contaminants. Three of the four participant cohorts (Asturias, Gipuzkoa, and Valencia) had information on both maternal and cord serum OC concentrations. Table 3 shows the Pearson correlation coefficients between maternal and cord log2(OC) concentrations expressed in ng/mL as well as in ng/g lipid (range, 0.38–0.77, p < 0.001 in all cases). Maternal serum concentrations (nanograms per milliliter) of DDE, HCB, and PCBs 138, 153, and 180 averaged 2.46, 2.11, 2.41, 2.55, and 2.79 times those of cord serum, respectively. Ratios were close to 1 when OC concentrations were lipid-adjusted (Table 3). In the Supplemental Material, Table S3 shows the Pearson’s correlations between OCs in the same matrix (p < 0.001 in all cases) being similar using the weight and the lipid-adjusted concentrations. Correlations were lower between DDE and other OCs (ranges, 0.12–0.27 and 0.31–0.39 in maternal and cord serum, respectively), and higher between HCB and PCBs or between PCB congeners (ranges, 0.53–0.88 and 0.54–0.82 in maternal and cord serum, respectively).

OC exposure and ultrasound measurements of fetal growth. In Figure 1, the adjusted regression analyses are shown for the relationship between log2(OC) concentrations measured in either maternal or cord serum samples and SD scores of fetal growth or size (percent of change; 95% CI, for a doubling in OCs).

Between 0 and 12 weeks of pregnancy, there were not statistically significant associations between OC concentrations and fetal outcomes except in the case of cord HCB (–2.3%; 95% CI: –4.4, –0.2%) or cord PCB-138 (–2.6%; 95% CI: –5.1, –0.1%) and AC growth. Marginally significant inverse associations (p < 0.10) were also found between cord HCB and EFW and between cord PCB-138 and the rest of fetal outcomes.

For the period between 12 and 20 weeks of gestation, we did not find any statistically significant associations between OC concentrations and growth of BPD or FL. Regarding AC growth, patterns were similar for maternal and cord serum (Figure 1), but only statistically significant for cord PCB-138 (–3.3%; 95% CI: –5.8, –0.8%) and PCB-180 (–3.7%; 95% CI: –6.5, –0.9%). Marginally significant inverse associations were also found between AC and the rest of OCs measured in cord (4,4'-DDE, HCB, and PCB-135). Associations for EFW growth did not reach statistical significance but were marginal with maternal PCBs 138 and 153.

For the period between 20 and 34 weeks of pregnancy, negative associations were observed for all the fetal outcomes and PCBS measured in either maternal or cord serum. These associations were significant for maternal PCB-138 and EFW growth (–2.1%; 95% CI: –4.2, –0.1%), maternal PCBs and FL growth (PCB-138: –2.8%; 95% CI: –4.9, –0.8%; PCB-153: –3.8%; 95% CI: –6.0, –1.6%; and PCB-180: –3.0%; 95% CI: –5.3, –0.3%) and cord PCBs and BPD growth (PCB-138: –2.8%; 95% CI: –5.3, –0.3%; and PCB-153: –3.1%; 95% CI: –6.0, –0.2%).

Patterns of associations on growth parameters were coherent with those observed on size at 34 weeks, but only some associations were statistically significant (Figure 1). Negative associations between cord PCBs 138 and 153 and growth in BPD between 20 and 34 weeks of gestation were also apparent for the same exposures and BPD size at 34 weeks, though the association with PCB-153 was only marginally significant. All three PCBs measured in maternal serum were associated with significantly lower FL growth between 20 and 34 weeks of gestation and smaller FL size at 34 weeks. Although AC growth was significantly lower in association with cord HCB and PCB-138 at 0–12 weeks, and with cord PCBs 138 and 180 at 12–20 weeks, AC size at week 34 was not clearly associated with either exposure. No significant associations between DDE and fetal growth were observed during pregnancy.

The estimates of the main analysis (i.e., multiple imputation) were similar to those of

### Table 2. Percentage ≥ LOD and median (P25, P75) of OCs (ng/mL): the INMA Project, 2003–2008 (Spain).

| Variable | 4,4'-DDE | HCB | PCB-138 | PCB-153 | PCB-180 |
|----------|----------|-----|---------|---------|---------|
| Overall % ≥ LOD | 99.2 | 93.2 | 90.9 | 96.2 | 93.6 |
| Overall (n = 2,369) | 0.83 (0.49, 1.56) | 0.29 (0.16, 0.51) | 0.17 (0.11, 0.25) | 0.28 (0.19, 0.40) | 0.20 (0.13, 0.30) |
| Asturias (n = 450) | 1.39 (0.80, 2.41) | 0.37 (0.22, 0.58) | 0.20 (0.14, 0.29) | 0.34 (0.24, 0.45) | 0.24 (0.16, 0.34) |
| Gipuzkoa (n = 566) | 0.54 (0.35, 0.84) | 0.20 (0.12, 0.32) | 0.18 (0.13, 0.26) | 0.30 (0.21, 0.43) | 0.22 (0.14, 0.34) |
| Valencia (n = 594) | 0.71 (0.43, 1.16) | 0.23 (0.13, 0.38) | 0.11 (0.07, 0.16) | 0.20 (0.14, 0.28) | 0.14 (0.09, 0.20) |
| Overall (n = 450) | 1.39 (0.80, 2.41) | 0.37 (0.22, 0.58) | 0.20 (0.14, 0.29) | 0.34 (0.24, 0.45) | 0.24 (0.16, 0.34) |
| Overall (n = 594) | 0.71 (0.43, 1.16) | 0.23 (0.13, 0.38) | 0.11 (0.07, 0.16) | 0.20 (0.14, 0.28) | 0.14 (0.09, 0.20) |
| Overall (n = 596) | 0.54 (0.35, 0.84) | 0.20 (0.12, 0.32) | 0.18 (0.13, 0.26) | 0.30 (0.21, 0.43) | 0.22 (0.14, 0.34) |

### Table 3. Concentration ratios and Pearson correlations of OCs in maternal and umbilical cord serum (n = 1,102; the INMA Project, 2003–2008 (Spain)).

| OC | Expressed in ng/mL | Expressed in ng/g lipid |
|----|--------------------|------------------------|
| Ratio* C_m/C_u | Pearson coefficient |
| Median (P25, P75) |
| DDE | 2.46 (1.98, 3.21) | 0.77 | 1.04 (0.76, 1.48) |
| HCB | 2.11 (1.49, 2.94) | 0.57 | 0.88 (0.56, 1.36) |
| PCB-138 | 2.41 (1.69, 3.28) | 0.41 | 1.01 (0.67, 1.47) |
| PCB-153 | 2.55 (1.93, 3.45) | 0.40 | 1.11 (0.79, 1.52) |
| PCB-180 | 2.79 (1.96, 4.07) | 0.56 | 1.19 (0.79, 1.79) |

*Ratio C_m/C_u: ratio of maternal/cord concentrations in raw scale. Pearson correlation coefficient between maternal and cord OC concentrations in log scale (adjusted by cohort), p < 0.001 in all the Pearson correlations.

Abbreviations: DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; LOD, limit of detection; OC, organochlorine compound; P, percentile; PCB, polychlorinated biphenyl.
the complete case analysis (i.e., restricted to data with no missing information in covariates and OC values < LOD replaced with LOD/2 value), the multi-pollutant analysis (i.e., main analysis including other OCs), or the main analysis excluding GWG (Figure 2; see also Supplemental Material, Figures S5–S7). The main differences were found in the multi-pollutant analysis with wider CIs. There were no consistent interactions with sex (data not shown), and only two interactions were statistically significant: cord HCB and FL growth between 12 and 20 weeks of pregnancy (females: –1.9%; 95% CI: –4.9, 1.0%, and males: 2.3%; 95% CI: –0.4, 5.0%, p-interaction = 0.03) and maternal 4,4´-DDE and AC growth between 20 and 34 weeks of gestation (females: 1.5%; 95% CI: –0.6, 3.5%, and males: –1.2%; 95% CI: –2.9, 0.6%, p-interaction = 0.05).

Discussion

To the best of our knowledge, this is the first study to consider specific fetal body segments that could be affected by exposure to OCs during different critical exposure windows. Increases in PCB concentrations were related to reductions in AC up to mid-pregnancy, and to decreases in fetal BPD and FL from gestational week 20 onward. We also found an inverse association between HCB and AC during the first trimester of pregnancy. The estimated mean difference in these fetal parameters ranged from –4% to –2% for a doubling in the OC concentrations. The magnitudes of the estimates in the multiple imputation analysis were similar to those of the complete case analysis, as well as those of the multiple imputation analysis after adding other OCs or excluding GWG. Clear results suggesting a differential effect between sexes were not found.

No associations between serum DDE concentrations and ultrasound measurements were found. No previous studies using fetal anthropology measures are available for comparison with our results, but controversy exists about birth size. Although associations were reported in some studies (Lopez-Espinosa et al. 2011; Wolff et al. 2007), others found little or no evidence of associations with DDE exposure (Govarts et al. 2012; Sagiv et al. 2007).

Cord serum HCB concentrations were inversely associated with AC in early pregnancy. Although this fetal measure and birth weight are not directly comparable, a marginally significant decrease in birth weight associated to cord HCB concentrations was reported in newborns from the INMA-Valencia cohort (Lopez-Espinosa et al. 2011). Additionally, a non-statistically significant inverse association between birth weight and maternal HCB concentrations was reported in another previous INMA study (Basterrechea et al. 2014).

Some PCBs measured in cord serum were negatively associated with AC. Specifically, this was the case with PCB-138 up to the second trimester and PCB-180 at 12–20 weeks of pregnancy. Despite the limitations of comparability between fetal and birth outcomes, a systematic analysis of 20 epidemiological studies on PCBs reported insufficient evidence of an association with birth weight < 2,500 g (El Majidi et al. 2012). Conversely, an inverse linear exposure–response relationship between birth weight and cord PCB-153 was reported in a meta-analysis conducted in 12 European cohorts, which include the children in the present study (Casas et al. 2015; Govarts et al. 2012). In a second analysis controlling for GWG, the strength of the association was reduced, although a statistically significant reduction in birth weight was still observed (Govarts et al. 2014). In the present study, maternal serum PCB-138, -153, and -180 concentrations were associated with lower FL growth from 20 to 34 weeks and smaller FL size at 34 weeks. Cord serum PCB-138 and -153 concentrations were associated with lower BPD growth from 20 to 34 weeks and smaller BPD size at 34 weeks (with the latter significant only for PCB-138). A marginally significant reduction in birth length...
associated with cord PCB-153 concentrations was previously found in the INMA-Valencia cohort (Lopez-Espinosa et al. 2011). Conversely, associations with birth length or head circumference were not found in other studies (Sagit et al. 2007; Wolff et al. 2007).

Although the biological mechanisms underlying the effects of OCS on fetal growth are not well established, these compounds can disrupt the endocrine system, which is involved in fetal development (Bouguignon and Parent 2010). Thus, thyroid hormones play an important role in somatic growth and in the differentiation and functioning of many tissues during development (Blazer et al. 2003), and some studies have suggested the existence of an association between altered thyroid levels during pregnancy and exposure to some OCS (Alvarez-Pedrerol et al. 2009; Lopez-Espinosa et al. 2009). OCS may also impede placental functions and contribute to fetal growth impairment. Thus, exposure to some OCS has been associated with placental vascular and trophoblastic lesions in animals studies (Bäcklin et al. 1998) and alterations of the placental transport of calcium and other nutrients in humans (Hamel et al. 2003; Tsuji et al. 2013) that are essential for fetal development.

Several shortcomings of the present study warrant cautious interpretation of the findings until more studies are available. Because multiple estimates were derived, results should be taken with caution: Some statistically significant associations could result from chance. The estimates of the coefficients and their confidence intervals should be taken as a global picture of the pattern of the relations between the variables involved in the study (Rothman 1990). Second, the criteria of inclusion may have imposed some selection and an underrepresentation of pregnant women with increased risk of adverse pregnancy outcomes. However, the aim of these commonly used criteria is to obtain a more homogeneous population and reduce the confounding potential. Another weakness is the possible selection bias between women included in or excluded from the present study, yet the differences in the main study variables observed between both groups were not significant. Although the OC concentrations were measured in two different laboratories with different LODs, both participated in the same monitoring and assessment program for persistent organic pollutants in human serum to verify their analytical results and to ensure the comparability of their data. In addition, random-effects meta-analysis was used to address heterogeneity resulting from the use of different laboratories and other factors that could differ among the cohorts.

One of the major strengths of this work with respect to previous studies on birth size is the repeated measurements of fetal anthropometry, which allowed us to study associations between OCS and growth in different stages of pregnancy. We accurately assessed fetal growth by means of a longitudinal analysis, adjusting for parental and fetal characteristics, to compare the expected versus real growth of each fetus. The use of individualized standards is expected to reduce misclassification by identifying constitutionally small babies and those with restricted growth (Gardosi 2004). Second, the use of repeated measurements of fetal anthropometry allowed us to study associations between these growth parameters and OCS in different stages of pregnancy, and thereby identify critical periods within gestation. Third, unlike most previous studies that have relied on a single blood measurement of exposure, we had information on OC exposure at the beginning of pregnancy and at delivery. Finally, other strengths of the present study are the large sample size, its prospective

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**Figure 2.** Sensitivity analysis of the association between OC concentrations and fetal size at 34 weeks of gestation: the INMA Project, 2003–2008 (Spain). Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; DDE, dichlorodiphenyldichloroethylene; EFW, estimated fetal weight; FL, femur length; GWG, gestational weight gain; HCB, hexachlorobenzene; OC, organochlorine compound; PCB, polychlorinated biphenyl. Adjusted linear regression models between log2(OC) concentrations and fetal growth (Gardosi 2004). Second, the use of

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*GWG was not included in models of maternal OCS and outcomes measured at week 12 because GWG was calculated from week 12 to delivery.*
design, the low rate of participant dropout between recruitment and delivery, detailed information on many potential confounders from early pregnancy, and the use of multiple imputation to deal with undetected values in the exposure variables and missing values in the covariates (Sterne et al. 2009).

Conclusions

PCB exposure may decrease fetal AC growth during the first two trimesters of pregnancy, and fetal growth of BPD and FL from mid-pregnancy onward. A transient association between HCB and AC in early pregnancy was also found. The reduction of these parameters ranged from −4% to −2% for a doubling in the OC levels. No statistically significant association between DDE and fetal growth was observed. Ultrasonogram measurements constitute a promising tool to examine how early prenatal OC exposure may affect fetal growth and more studies are needed.

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