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Maternal dietary intake of polyunsaturated fatty acids modifies association between prenatal DDT exposure and child neurodevelopment: A cohort study☆

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ABSTRACT

Background: Maternal 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) serum levels during pregnancy have been negatively linked to child neurodevelopment in contrast to intake of omega-3 and -6 (ω-3 and ω-6) fatty acids.
Objectives: To assess whether maternal dietary intake of ω-3 and ω-6 during pregnancy modifies the association between exposure to DDE and child neurodevelopment from age 42–60 months.
Methods: Prospective cohort study with 142 mother–child pairs performed in Mexico. DDE serum levels were determined by electron capture gas chromatography. Dietary ω-3 and ω-6 intake was estimated by questionnaire. Child neurodevelopment was assessed by McCarthy Scales.
Results: Docosahexaenoic (DHA) fatty acid intake significantly modified the association between DDE and motor component: increased maternal DDE was associated with lower motor development in children whose mothers had lower DHA intake ($\beta_{log2DDE} = -1.25$; 95% CI: −2.62, 0.12), in contrast to the non-significant increase among children whose mothers had higher DHA intake ($\beta_{log2DDE\text{-}motor} = 0.50$; 95% CI: *0.55, 1.56*). Likewise, arachidonic fatty acid (ARA) intake modified the association between DDE and memory component: increased maternal DDE was associated with a significantly larger reduction in the memory component in children whose mothers had lower ARA intake ($\beta_{log2DDE} = -1.31$; 95% CI: −2.29, −0.32) than children whose mothers had higher ARA intake ($\beta_{log2DDE\text{-}memory} = 0.17$; 95% CI: −0.78, 1.11).
Conclusions: Dietary intake of DHA and ARA during pregnancy may protect against child neurodevelopment damage associated with prenatal maternal DDE levels.

1. Background

Polyunsaturated fatty acids (PUFAs) are essential nutrients with neuroprotective activity. They constitute up to 35% of total lipids in the brain. PUFAs promote synaptic plasticity and stimulate dendritic arborization and formation of new spines. The most common omega-3 (ω-3) and omega-6 (ω-6) dietary PUFAs are α-linolenic (ALA) and linoleic (LA) acids. The main metabolites of ALA are eicosapentaenoic (EPA), docosapentaenoic (DPA), and

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docosahexaenoic (DHA) fatty acids whereas the main metabolite of LA is arachidonic acid (ARA). The principal dietary source of ω-3 is fish and, to a lesser extent, some vegetable oils (linseed, soybean, canola, and walnut). Dietary intake of vegetables, meat, eggs, corn and safflower oils are important sources of ω-6 (Benatti et al., 2004; Crupi et al., 2013). The fetus receives PUFAs from the mother's diet through placental diffusion whereas breastfeeding is the main source during postnatal life (Fleith and Clandinin, 2005).

Deficiency of certain fatty acids has been associated with disruption of neurologic and visual development across species (Davis-Bruno and Tassinari, 2011). In addition, prospective cohort studies have suggested that maternal intake of PUFAs promotes child neurodevelopment (Ryan et al., 2010). In a recent cohort study of premature infants, DHA and ARA infant plasma concentrations were positively associated with their neurodevelopment between 6 and 18 months of age (Sabel et al., 2012). However, evidence from randomized clinical trials has been suggestive but inconclusive regarding the benefits for child neurodevelopment of PUFA supplementation during pregnancy and/or breastfeeding (Campoy et al., 2012).

DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane), is a lipophilic compound with high persistence in the environment, with a half-life of approximately 10 years (Wolff et al., 2007). DDT was widely used in Mexico and was not banned until the year 2000 (Chanon et al., 2003). Our research group has shown that maternal serum concentrations of 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE), the main metabolite of DDT, during the third trimester of pregnancy are significantly and negatively associated with the general cognitive index (GCI) as well as the numerical, verbal, and memory components of the McCarthy Scales of Children's Abilities (MSCA), in children aged 42–60 months (Torres-Sánchez et al., 2013).

The aim of this study was to test our hypothesis that maternal dietary intake of PUFAs during pregnancy modifies the negative association between prenatal DDE exposure during the third trimester and child neurodevelopment between 42 and 60 months of age.

2. Materials and methods

Between January 2001 and June 2009, a prospective perinatal cohort study was conducted to evaluate the association between prenatal maternal DDE serum levels and child neurodevelopment. Detailed information about cohort assembling and follow-up has been published elsewhere (Torres-Sánchez et al. 2007, 2013).

Briefly, 1585 women were identified during prenuptial talks required to perform civil marriage in four municipalities of Morelos state, Mexico. Eligible women had no history of chronic diseases and were not being treated with anticonvulsants. Those women who agreed to participate (n = 996) and signed an informed consent letter were contacted every 8 weeks to detect early pregnancies and were interviewed regarding sociodemographic, reproductive, and dietary characteristics. Women that became pregnant (n = 517) were followed up to assess their pregnancy evolution in each trimester, as well as their dietary characteristics and DDE serum levels. At the end of their pregnancy, 442 women remained in the cohort (75 follow-up losses = 14.5%).

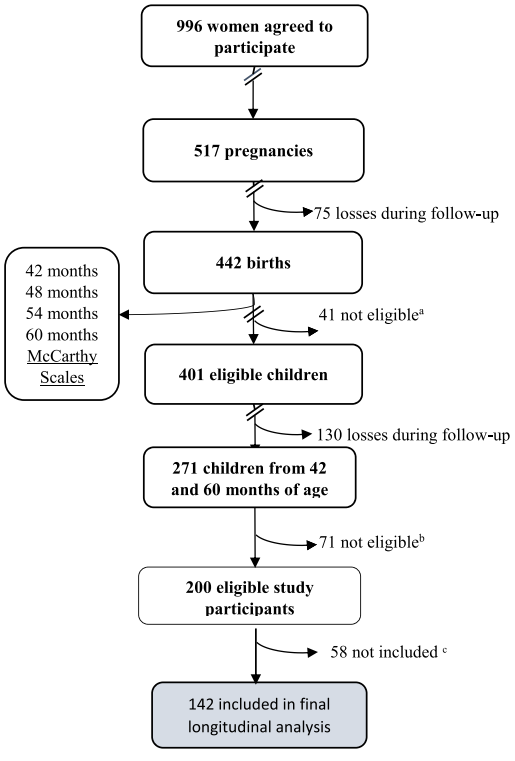
Of 442 births, 41 newborns were not eligible according to one or more of the following criteria: prematurity (≤37 weeks), low birth weight (≤2 kg), twin birth, cerebral atrophy, birth defects, or perinatal asphyxia. Children were enrolled in the cohort from 2001 to 2006 and followed up until 2009 to evaluate their growth, (weight and size) as well as their neurodevelopment at 1, 3, 6, 12, 24, 30, 42, 48, 54, and 60 months of age. During the follow-up period, 8.7% (35/401) of participants dropped out of the study by age 1 month, 8.5% (31/366) by age 12 months, 10.7% (36/335) by age 24 months, 7.0% (21/299) by age 42 months, and 2.5% (7/278) by age 60 months.

From a total of 271 children remaining after 5 years of follow-up (278-7 children), 200 that fulfilled the following criteria were eligible for this study: at least one measurement of maternal serum DDE, at least one evaluation of maternal diet during pregnancy, at least 500 Kcal of mothers' daily intake, and at least two evaluations of child's neurodevelopment between 42 and 60 months of age. From them, 142 children whose mothers had a DDE measurement during the third trimester were included in multivariate analysis (Fig. 1).

This study was approved by the Ethics Committee of the National Institute of Public Health of Mexico.

2.1. Child neurodevelopment

The MSCA was used to assess child neurodevelopment between 42 and 60 months. This instrument evaluates cognitive and motor development across five subscales: motor, memory, perceptual, numerical, and verbal; the last three subscales conform to the GCI, which is equivalent to the intellectual quotient (IQ) assessment provided by other tests. The MSCA Spanish version validated in Spain, was used in this study. An average score of 100 ± 16 points for GCI and 50 ± 10 points for other components were considered references (McCarthy, 2006). The MSCA was administered by three psychologists, whose results had an interobserver reproducibility of 0.99 (Torres-Sánchez et al., 2013). Psychologists were blinded to prenatal DDE exposure status and maternal fatty acid intake during



[a] Prematurity (≤ 37 weeks), low birth weight (≤ 2 kg), twin birth, cerebral atrophy, birth defects, or perinatal asphyxia.
[b] Less than two McCarthy evaluations, no maternal serum DDE evaluations, no dietary information in any trimester of pregnancy, and maternal energy intake < 500 Kcal/day.
[c] No maternal serum DDE evaluation during the third trimester.

Fig. 1. Study population selection pathway.