行政院國家科學委員會專題研究計畫 成果報告

環境職業生殖發育危害（七）—探討子宮內陶斯松暴露對胎兒成長及新生兒神經行為發育之影響
研究成果報告(精簡版)

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行政院國家科學委員會補助專題研究計畫 ■ 成果報告
□期中進度報告

環境職業生殖發育危害（七）—探討子宮內陶斯松暴露對胎兒成長及新生兒神經行為發育之影響

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摘要

研究背景：農藥在世界上已被大量使用，而其主要用途是用來作為預防及殺死害蟲及用在農田作物上或居家的蟲害控制。在台灣，每年大約有 500 種農藥被允許使用，其使用量每年大約有 1 萬公噸。在 2003 台灣使用最大量的農藥是有機磷殺蟲劑，其中更以陶斯松的使用量為最多。此種非持續性農藥被使用在室內及室外、都市及鄉村地區，在食物、飲用水、農田、家中及學校中都能被發現。在室內的使用後，有機磷農藥都還能穩定的持續幾天或幾星期。以陶斯松為例，在室內噴灑後其還能持續至少兩週以上。而其暴露可能的健康影響有許多仍尚不清楚，特別是對於小孩的健康影響，因此探討其健康危害就很重要。目前有三個美國的研究指出農藥暴露對於出生體重，頭圍，身長及出生週數有些微影響但並未一致的結論。而其對於神經行為發展的影響在人類流行病學研究上是欠缺且無定論的。農藥暴露與個體之基因多型性之交互作用對嬰兒生長及神經行為發展之影響目前亦尚無定論。因此研究目的即為探討有陶斯松暴露對於嬰兒生長及神經行為發展的影響。

研究設計：此研究設計是一橫斷性的研究。研究的族群是在 2004 年 5 月至 2005 年 1 月在臺北縣市生產的孕婦及其嬰兒共 81 對。為了控制其他可能的影響出生結果的危險因子，我們剔除產婦年齡低於 18 歲或高於 40 歲、有抽煙史的產婦。我們在其產前即將其列入研究，並以結構性問卷進行問卷訪視、並收集母親血液及新生兒臍帶血並分離 DNA，並分析血中陶斯松濃度及 PON1 基因多型性，最後我們透過複迴歸統計方法探討暴露對出生結果及神經行為發展的影響。

結果：臍帶血中陶斯松的濃度有 9 位個案的濃度大於偵測極限 0.4 ppb，其的中位數是 1.29 ppb。複線性迴歸統計結果發現，較高的臍帶血陶斯松濃度和較短的出生身長有顯著的相關(OR = 5.86, 95% CI = 1.68 to 20.43)。而邏輯斯迴歸結果也顯示較高的臍帶血陶斯松濃度和較低出生身長及 SGA 有關(OR = 13.22, 95% CI = 1.3 to 134.4)。但是在新生兒神經行為發展上及 PON1 基因多型性並未看到顯著的影響。

結論：陶斯松暴露對於嬰兒成長的有所影響，未來將持續追蹤此族群以探討陶斯松暴露對於幼兒神經形為發展的影響。

關鍵詞：有機磷、陶斯松、出生結果、出生體重、頭圍、身長、出生週數、神經行為、PON1 基因多型性

Abstract

Background: Organophosphates were the largest amount of used pesticides in Taiwan in 2003, and chlorpyrifos was the most one. These pesticides were used indoors and outdoors in either urban or rural areas, and could be found in food, water, agricultures, homes, and schools. In the indoor settings, they could still remain stable for days or weeks; for example, chlorpyrifos could persist for at least two weeks after spreading. The potential health effect was still unknown, and exploring the health effect was important. Only three recent studies in the U.S. had reported inconsistent and slightly effect on birth weight, head circumference, birth length and gestational age. The effect for neurodevelopment on human study was absence and unconcluded. Thus, the aim of the study was to explore the risk of chlorpyrifos pesticide on fetal growth and neurodevelopment.

Material and Methods: This study was a cross-sectional in design. The study populations

were the mothers who gave births in Taipei between May 2004 and January 2005 and their infants. A total of 81 pregnancy women were included in the study. To control potential risk factors for adverse birth outcomes, we excluded women if they were younger than 18 years old or older then 40 years old, or had the history of cigarette smoking. We enrolled them before delivery, interviewed by a structured questionnaire, and collected mother's blood and umbilical cord blood and separate DNA to analysis chlorpyrifos concentration in blood and gene SNPs. We shall use multiple regression models to explore the effect of chlorpyrifos exposure on birth outcomes and neurodevelopment.
Results: The median chlorpyrifos concentration was 1.29 ppb in 9 neonates whose concentrations were higher than the detection limit of 0.4 ppb. There were negative relations between cord plasma chlorpyrifos and short birth length (OR = 5.86, 95% CI = 1.68 to 20.43) and small for gestational age (OR = 13.22, 95% CI = 1.3 to 134.4). However, we didn't find any significant effects of chlorpyrifos in cord blood on the neonatal neurobehavioral examination or modification effect of PON1 polymorphism.
Conclusions: Chlorpyrifos exposure in the general population may be related to reduce fetal growth. We're going to follow-up these newborns to investigate any potentially prenatal exposure delayed effect.

Keywords: organophosphates, chlorpyrifos, birth outcomes, birth weight, head circumference, birth length, gestational age, neurobehavioral development, PON1 polymorphism

Introduction

Quite a few animal data suggested that the low-level exposure to certain organophosphates (including chlorpyrifos and diazinon) during pregnancy or early life could cause the risk of retardation of the fetal growth and neurocognitive development in the offspring although little is known about the effects of residential pesticide exposure among human population . Birth weight decrease at high exposure levels, but not at low exposure levels, was observed in a two-generation reproductive study of propoxur in the rat experiments. Exposing rodent dams to certain organophosphate pesticides, such as chlorpyrifos, quinalphos, and dimethoate, during pregnancy was found to be associated with the decrements in fetal growth in several studies. Whyatt et al. studied the pesticide exposure and the birth outcomes in New York City and they found that insecticides were detected in 45–74% of blood samples collected from the mothers and newborns at delivery and maternal and newborn levels were highly correlated. This study has indicated the pesticides could be transferred from the mother to the fetus during pregnancy. They concluded that prenatal chlorpyrifos exposure might cause impairment of the fetal growth and that diazinon exposure might be an attributable factor to the effects. Recently year in the United States, there were three studies had exploring the risk of some pesticides exposure during pregnancy on birth outcomes. They were all prospective cohort study in design, and collected the specimens (urine, blood and cord blood) to evaluate the internal dose of exposure. They had found that exposure to potential pesticides were related to decrease birth weight, birth length, decrease head circumference, and decreased gestational age.

The organophosphate pesticides were also neurotoxins, and the detrimental effects on neurodevelopment had shown in animals. Experimental evidence had linked organophosphate exposure during gestation or the early postnatal period to adverse neurodevelopment squealed in offspring. In human study, Young et al. had demonstrated that no detrimental associations were found between postnatal urinary metabolite levels and any of the Brazelton Neonatal Behavioral Assessment Scale (BNBAS). But the association with increasing urinary metabolite levels was observed for both increase on number of abnormal reflexes and the proportion of infant with more than three abnormal reflexes. Therefore, the objective of this

study was to exploring the health effect of in utero chlorpyrifos exposure on birth outcomes and neurodevelopment.

Materials and Methods

Study population and design

This study was a cross-sectional in design. The study subjects were from the Taiwan Birth Panel study (TBPS) that carried out during 2004 and 2005 including mother-infant paired. The study populations were collected in one medical hospital in Taipei city, one area hospital, and two clinics in the Taipei County. Protocols used in this study were approved by the Ethical Committee of National Taiwan University Hospital. A total of 81 pregnancy women were included in this study. Before enrolled the study populations, inform consents were obtain from them, including study aim, specimens collection and questionnaire were interpretation of them too. To control potential risk factors for adverse birth outcomes, we just included women age between 18 to 40 years old, and not had history of cigarette smoking. They were enrolled before delivery, interviewed by a structured questionnaire, and collected mother's blood and umbilical cord blood.

Biological sample collection and analysis

In order to measure the internal dose directly, subjects' specimen was assembled for biological monitoring. Newborn's cord blood (40 ml) was collected as closed to delivery by the hospital stuff. All the blood were added EDTA to avoid clotting. The collected samples were transported to laboratory immediately and separated into buffy coat, plasma and DNA within forty-eight hours. Within twenty-four hours the specimens were stored at -80℃ before analysis. The plasma chlorpyrifos concentration were analyzed using gas chromatography coupled to tandem mass spectrometry in Taiwan agricultural chemicals and toxic substances research institute council of agriculture (TACTRI/COA). It was analyzed by GC-MS-MS. The detection limited of this method is 0.4 ppb.

Neurodevelopment

Within three days after delivery, the Neonatal Neurobehavioral Examination in Chinese Version (NNE-C) was performed to detect neonatal neurobehavioral. The NNE-C scale consisted of three parts: behavioral responses, tone and motor patterns, primitive reflexes, and each part contains nine items to test. The entire test was performed by a trained nurse and a physical therapist. Jeng et al. had demonstrated that the NNE-C scale had used the Cronbach's alpha coefficient to establish the internal consistency and the value for the whole was 0.84. (Jeng et al. 1996; Jeng et al. 1998) They concluded that the NNE-C scale was clinically feasible and reliable for the evaluation of neurobehavioral functions of infants in Chinese-speaking societies. The result of the testing was combined with the pesticides exposure data to evaluate the health effect.

Genotyping

Genomic DNA was isolated from blood using the chemagic DNA blood kit special (Chemagen, Aachen, Germany) following the manufacture's protocol. Method for determining genotypes PON1 –162AG, 55LM, and 192QR polymorphisms were using real-time polymerase chain reaction as previously described (Pocsai et al. 2003). Briefly, the polymorphisms of PON1 192QR and 55LM in the coding region and –162AG in the promoter region were performed on a lightCycler^{TM} 480 instrument (Roche, Mannheim, Germany). This method was described previously by using hybridization probes in combination with lightCycler^{TM} DNA Master Hybridization probes kit (Roche, Mannheim, Germany). Both the PCR primers and the fluorescent-labeled detection probes were

synthesized by TIB MOLBIOL, Berlin, Germany. The 45 cycles amplification were performed by following steps: 95 °C for 10 s, 60 °C for 20 s and 72 °C for 10 s. After the amplification, melting curves were performed by heating the samples at 95 °C for 1 min using a ramping rate of 4.4 °C/s, holding them at 40 °C for 1 min in order to get maximum hybridization, then slowly heating the reaction mixtures up to 75 °C. Melting curve analysis was generated using lightCycler^{TM} 480 Software.

Statistical analysis

The major outcomes interested in this study were birth outcomes and neurological parameters for infants, including birth weight, head circumference, chest circumference, length, gestational age at birth, small for gestational age (SGA), and the neurobehavioral development at birth. We conducted multiple linear regression and logistic regression analyses to evaluate the relation between the births outcomes and neonatal neurobehavioral with chlorpyrifos concentration in the cord blood. Chlorpyrifos concentrations in the cord blood were log-transformed before analysis to normalize the pesticides levels. Values below the LOD were assigned a value of half the LOD. (Lubin et al. 2004) For logistic regression analysis, the birth weight, head circumference, chest circumference, length, gestational age at birth, SGA, and the NNE-C scale were categorized by using 15 percentile values as the cut-point value to evaluate the poor or good development and performance.

Results

The study population consisted of 81 mother-infant pairs. Base on the cord plasma chlorpyrifos concentrations, we grouped the study population into three groups. One was above the DL, another one was had detected chlorpyrifos but below the DL, the other one was not detected chlorpyrifos in the plasma, and defined them as the high, middle and low exposure group. There are 9, 13 and 59 people in it and the DL and DL/2 was given as the concentration in middle and low group.

Table 1 present the demographics of mothers. Comparing the questionnaire variable pesticides used by household member, with the cord plasma concentration, there was low correlated. Table 2 shows the distribution of infant characteristic, infant exposure and birth outcomes and neurodevelopment. The birth outcomes were used 15 percentiles as cut-points and had show in table 2. For exposure data, the median and interquartile ranges (IQR) in the high level group were 1.29 and 0.75. There were all had the completed birth outcomes data, but only 54 infants had the NNE-C scale. The PON1 –162AG, 55LM, and 192QR polymorphisms frequency and the relation with birth outcomes were showed in table 3. Table 4 was the linear model for birth outcomes and neonatal neurodevelopment and cord blood chlorpyrifos levels. We use the ten percent change in estimate to decide the related covariate should or not taken into the final model. Higher chlorpyrifos concentrations in umbilical cord blood were associated with significantly shorter birth length and less birth weight, after controlling the confounders. The categorized analysis for logistic regression was show in table 4. High chlorpyrifos levels were also associated with increase risk of birth length (adjusted odds ratio = 5.86, 95% CI: 1.68, 20.43) and SGA (adjusted odds ratio = 13.22, 95% CI: 1.30, 134.4).

Discussion

In this general population of Taiwan, there were 11% subjects above our detection limit of 0.4 ppb chlorpyrifos concentration. We also found that the cord plasma concentration was related to increase small for gestational in addition to decreased birth weight and length. However, no significant result was detected on neonatal neurodevelopment.

The cord plasma chlorpyrifos concentrations in neonates in this study were higher

concentrations those in the studies of United States. Comparing with the New York City study, they had much higher percentage samples were non-detectable and it was due to we had higher detection limit, in our study was 0.4 ppb and in New York City study was 1.0 ppt. But comparing the median concentration of these two studies, we had much higher concentration than the New York City study, 1.29 ppb in our study and 2.6 ppt in New York City study in cord plasma. (Whyatt et al. 2003) As the result, we should take more concern on the potential exposure sources.

For biomonitoring, we used cord plasmas as the markers to evaluate the exposure dose and analysis chlorpyrifos directly. The advantage taking blood as media was it was regular fluid, the blood concentrations of toxicant will remain the same as long as the absorbed amounts were constant; thus, unlike urine, which was not regulated, no corrections for dilution were necessary. (Barr et al. 1999) In plasma samples, the chlorpyrifos and 3,5,6-trichloro-2-pyridinol (TCPy) were mostly ones used to analysis the chlorpyrifos exposure concentrations. Analyzed the chlorpyrifos had some advantage than TCPy. The TCPy was the pesticides-specific metabolites for chlorpyrifos, chlorpyrifos-methyl and other chemicals, but for risk assessment, distinguishing between exposures to each pesticide was very important. (Barr et al. 2002) Once absorbed, the insecticides appear to be rapid eliminated with biological half-lives on the order of hours to days in adults. (Barr et al. 2002) But the data of chlorpyrifos biological half-life in the fetus were lacked. In an animal study, the biological half-lives of blood chlorpyrifos and TCPy are 8.15 and 24.66 h. (Sunaga et al. 1989) However, limitation for the biomarker was the blood sample collected at a single time point only, they would not clear to what extent these measurements reflect exposure over critical window during pregnancy. However, in the indoor settings it could remain stable for a certain period of time after application, about two weeks. (Gurunathan et al. 1998) Moreover, the exposure could be sustained and stable, such as chronic exposure, if the chlorpyrifos exposure was from environment.

We also found that decreases in birth weight and birth length were associated with cord plasma chlorpyrifos. Recently in the United States, there were three studies exploring the risk of pesticide exposures including chlorpyrifos during pregnancy on birth outcomes. They were prospective in design, and collected specimens (urine, blood and cord blood) to evaluate the internal dose of exposure. (Whyatt et al. 2004; Whyatt et al. 2003; Berkowitz et al. 2004; Eskenazi et al. 2004; Perera et al. 2003; Berkowitz et al. 2003) They had found that exposure to potential pesticides were related to decrease birth weight, birth length, decrease head circumference, and decreased gestational age. Otherwise, Margarita et al. also had reported that a significant association between the positive exposure to pesticides and the presence of intrauterine growth retardation (IUGR) by testing blood AChE. (Levario-Carrillo et al. 2004) We could not find any relation to head circumference at birth and their neonatal neurodevelopment.

For neurodevelopment, there was showed no adverse effect on chlorpyrifos. But in previous study, the animals experiencing in utero OP exposure demonstrate decreased balance, increased righting reflex time and poorer cliff avoidance. (Chanda et al. 1995; Chanda et al. 1996) Young et al. had found the association with increasing urinary metabolite levels with both increase on number of abnormal reflexes and the proportion of infant. (Young et al. 2005) In our study, we might try to evaluate the three parts test of NNE-C separated to exploring the health effect and increasing sample size.

The organophosphate was also neurotoxins, and the detrimental effects on neurodevelopment had shown in animals. (Vidair et al. 2004) Experimental evidence had linked organophosphate exposure during gestation or the early postnatal period to adverse neurodevelopment squealed in offspring. (Johnson et al. 1998) In human study, Young et al.

had demonstrated the association with increasing urinary metabolite levels was observed for both increase on number of abnormal reflexes and the proportion of infant with more than three abnormal reflexes. (Young et al. 2005)

The limitations of the study were that it was cross-section in design. The causal relation between exposure and outcome was not clear. And in the biological marker, we just analyzed chlorpyrifos but not other kinds of pesticides. We did know the correlation with other pesticides, as the reason, we should not confirm the health effects were just due to chlorpyrifos exposure. From the result of this study, we should take additional research to confirm the health effect of pesticides exposure, and the follow the exposed infant to evaluate the health effect.

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Table 1. Maternal characteristics by umbilical blood chlorpyrifos levels

Characteristics	Umbilical blood Chlorpyrifos (μg/L)	
	< 0.4	≥ 0.4
Total	59	22
Age (years)		
<30	17	5
Maternal education		
Senior high school & below	38	9
Annual family income (NT$)		
<600,000	24	8
≥600,000	34	14
Environmental tobacco smoke		
Yes	33	18
Household insecticide use		
Yes	39	14
Weight before pregnancy (kg)		
Mean ±SD	53.7 ± 10.3	53.1 ± 7.3

Table 2. Fetal growth and neonatal neurodevelopment by umbilical blood chlorpyrifos levels

Characteristics	Umbilical blood Chlorpyrifos (μg/L)	
	< 0.4	≥ 0.4
Infant sex		
Male	20	10
Female	39	12
Fetal growth		
Gestational age (wks)	38.3 ± 1.4	38.4 ± 1.4
≤ 37 (%)	28.8	22.7
Birth weight (g)	3265.5 ± 469.7	3147.7 ± 400.5
< 2500 (%)	5.1	4.5
Small for gestational age (%)	3.4	18.2
Birth length (cm)	49.9 ± 1.9	48.9 ± 1.7
Head circumference (cm)	33.5 ± 1.7	33.6 ± 1.2
Chest circumference (cm)	32.6 ± 1.9	32.4 ± 1.3

Table 3. Infant PON1 polymorphism frequencies

Position and genotype	Polymorphism frequencies	Birth outcomes			
Infant polymorphism	N (%)	Gestational age (wks)	Birth weight (g)	Birth length (cm)	Head circumference (cm)
-162					
AA	3 (4.2)	37.0 ±1.0	2990.0 ±276.2	49.7 ±2.9	33.3 ±0.6
AG	14 (19.7)	38.1 ±1.4	3328.3 ±500.1	49.7 ±1.7	33.3 ±1.3
GG	54 (76.1)	38.3 ±1.4	3211.8 ±468.5	49.7 ±1.9	33.5 ±1.7
55					
LL	62 (91.2)	38.2 ±1.5	3215.6 ±476.5	49.7 ±2.0	33.4 ±1.6
LM	5 (7.4)	38.6 ±0.5	3302.0 ±368.3	49.8 ±1.3	33.4 ±1.3
MM	1 (1.5)	39.0	4062.0	51.0	37.0
192					
QQ	11 (14.9)	38.5 ±1.2	3243.1 ±460.2	49.6 ±1.2	33.9 ±1.8
QR	36 (48.6)	38.3 ±1.2	3304.9 ±513.2	49.8 ±2.2	33.6 ±1.2
RR	27 (36.5)	38.0 ±1.6	3109.9 ±384.2	49.5 ±1.7	33.0 ±1.9

Table 4. Crude and adjusted coefficients of log_{10} umbilical blood chlorpyrifos in μg/L for the continuous outcomes of fetal growth and neonatal neurodevelopment

Continuous outcomes	Coefficient ±standard error			
	Crude	*p* value	Adjusted	*p* value
Fetal growth				
Gestational age (wks)	0.65 ±0.55	0.24	0.39 [a] ±0.64	0.55
Birth weight (g)	-145.0 ±183.7	0.43	-207.2 [b] ±201.6	0.31
Birth length (cm)	-1.07 ±0.75	0.16	-1.50±0.70	0.03*
Head circumference (cm)	0.19 ±0.64	0.77	-0.57 [c] ±0.59	0.33
Chest circumference (cm)	-0.66 ±0.89	0.46	-0.64 [d] ±0.89	0.47
Neonatal neurodevelopment				
Neurobehavioral examination score	-0.65 ±1.32	0.62	-0.93 [e] ±1.19	0.43
Behavioral responses scale	-0.86 ±0.77	0.27	-0.51 [f] ±0.73	0.48
Tone and motor patterns scale	0.66 ±0.70	0.35	-0.44 [f] ±0.71	0.53
Primitive reflexes scale	-0.46 ±0.73	0.53	-0.13 [f] ±068	0.85

* $p < 0.05$.

[a] Adjusted for family income, weight gain during pregnancy

[b] Adjusted for environmental tobacco smoke, maternal education, weight before pregnancy, weight gain during pregnancy, and infant sex

[c] Adjusted for maternal age, education, environmental tobacco smoke, and weight before pregnancy, parity, infant sex, and gestational age.

[d] Adjusted for maternal age, education, environmental tobacco smoke, and weight before pregnancy.

[e] Adjusted for maternal age, education, family income, and environmental tobacco smoke, infant sex, gestational age, and technicians.

[f] Adjusted for maternal age, education, and environmental tobacco smoke, gestational age

Table 5. Crude and adjusted odds ratios for the categorical outcomes of fetal growth and neonatal neurodevelopment in ≥ 0.4 vs. < 0.4 μg/L umbilical blood chlorpyrifos

	Odds ratio (95% confidence interval)	
Categorical outcomes	Crude	Adjusted
Fetal growth		
Gestational age ≤ 37 wks	0.73 (0.23, 2.28)	0.55 (0.16, 1.89)
Birth weight ≤ 2800 g	1.24 (0.34, 4.51)	1.83 [a] (0.39, 8.39)
Small for gestational age < 15%	6.33 (1.07, 38.49)*	13.22[b] (1.3, 134.4)*
Head circumference ≤ 32 cm	0.32 (0.07, 1.55)	0.51[c] (0.09, 2.77)
Birth length ≤ 48 cm	3.63 (1.25,10.54)*	5.86[a] (1.68, 20.43)*
Chest circumference ≤ 31 cm	0.98 (0.23, 4.08)	0.63[a] (0.10, 3.72)
Neonatal neurodevelopment		
Neurobehavioral examination score ≤ 67	0.83 (0.19, 3.62)	1.05[d] (0.16, 7.04)
Behavioral responses scale ≤ 23	0.73 (0.17,3.11)	0.47[e] (0.07, 2.80)
Tone and motor patterns scale ≤ 22	0.50 (0.12, 2.09)	1.05[e] (0.19, 5.89)
Primitive reflexes scale ≤ 20	0.97 (0.22, 4.28)	0.47[e] (0.07, 2.82)

* p <0.05.
[a] Adjusted for gestational age.
[b] Adjusted for maternal weight before pregnancy and family income.
[c] Adjusted for maternal education and family income.
[d] Adjusted for gestational age and environmental tobacco smoke.
[e] Adjusted for gestational age, environmental tobacco smoke, and technicians.

Table 6. Adjusted coefficients of log_{10} umbilical blood chlorpyrifos in μg/L and infant PON1 polymorphism for the continuous outcomes of fetal growth

Continuous outcomes	Coefficient ±standard error			
	Umbilical blood Chlorpyrifos (μg/L)	p value	Infant polymorphism	p value
	≥ 0.4 vs. <0.4		PON1 –162AG	
Gestational age (wks)	-0.02 ±0.39	0.95	0.41 ±0.31	0.19
Birth weight (g)	-106.6 ±119.5	0.38	-69.6 ±96.3	0.47
Birth length (cm)	-0.96 ±0.48	0.05	-0.27 ±0.38	0.49
Head circumference (cm)	0.09 ±0.44	0.83	-0.01 ±-0.35	0.97
	≥ 0.4 vs. <0.4		PON155LM	
Gestational age (wks)	-0.04 ±0.40	0.91	0.47 ±0.64	0.47
Birth weight (g)	-103.8 ±122.2	0.40	136.8 ±193.8	0.48
Birth length (cm)	-0.91 ±0.49	0.07	-0.18 ±0.77	0.82
Head circumference (cm)	0.10 ±0.44	0.81	0.69 ±0.69	0.33
	≥ 0.4 vs. <0.4		PON1 192QR	
Gestational age (wks)	-0.04 ±0.38	0.92	-0.26 ±0.24	0.27
Birth weight (g)	-114.0 ±115.7	0.33	-50.3 ±73.7	0.50
Birth length (cm)	-1.05 ±0.46	0.03	0.08 ±0.29	0.79
Head circumference (cm)	0.09 ±0.41	0.83	-0.39 ±0.26	0.14

* p <0.05. Adjusted for infant sex and gestational age