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EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS AND NEWBORN BIOMETRIC INDICATORS

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Abstract
Objectives: The aim of the study was to examine the impact of polycyclic aromatic hydrocarbons (PAH) on foetal growth. **Materials and Methods:** The prospective Polish Mother and Child Cohort study was performed in 8 regions of Poland. The study population consisted of 449 mother-child pairs All women were interviewed three times during pregnancy (once in each trimester). 1-hydroxypyrene (1-HP) concentration in urine was chosen as the biomarker of exposure to PAH. The urine sample collected from the participant women between 20–24 weeks of pregnancy was analysed using high performance liquid chromatography (HPLC). The active and passive smoking exposure was verified by determination of saliva cotinine level using high performance liquid chromatography coupled with tandem mass spectrometry/positive electrospray ionisation (LC-ESI$^+$MS/MS) and isotope dilution method. **Results:** The exposure to PAH measured by 1-HP level in urine of pregnant women was significantly associated with child birth weight ($\beta = -158.3$; $p = 0.01$), chest circumference ($\beta = -0.7$; $p = 0.02$) and cephalisation index ($\beta = 4.2$; $p = 0.01$) after adjustment for gestational age, child gender, pregnant woman marital status, educational level, season of last menstruation period (LMP), prepregnancy body mass index (BMI), and weight gain in pregnancy. After inclusion salivary cotinine levels into the analysis, the results were not statistically significant. **Conclusions:** Prenatal exposures to PAH adversely influence foetal development including child weight, length, head and chest circumference. Tobacco smoking is the important source of PAH. After controlling for active and passive smoking, the observed associations were not statistically significant.

Key words:
Polycyclic aromatic hydrocarbons, Birth weight, Child length, Head and chest circumference, Cephalisation index

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAH) are ubiquitous air pollutants generated by combustion sources that include motor vehicles, coal-fired power plants and residential heating and cooking. Also tobacco smoking and environmental tobacco smoke (ETS) is a major source of PAH exposure.

There is widespread concern over the impact of PAH on pregnancy outcome [1–11]. A number of PAH are human mutagens and carcinogens and are potentially significant reproductive and developmental toxicants. Epidemiological studies indicated associations between PAH or PAH-DNA damage and foetal growth reduction [4,6,9]. The study conducted in Poland found that the newborns

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whose levels of PAH-DNA adducts were above the median (3.85/10^8 nucleotides) had significantly reduced birth weight, length, and head circumference [1]. An analysis performed in China indicated that high PAH-DNA adduct levels were associated with decreased birth head circumference and that the longer duration of prenatal exposure was associated with reduced birth length [12].

In the additional analysis made by Perera et al., B[a]P-DNA adducts were not significantly correlated with ETS or dietary PAH and B[a]P-DNA alone was not significantly associated with birth outcomes; however, there was a significant interaction between the two pollutants such that the combined exposure to high ETS and high adduct levels had a significant multiplicative effect on birth weight ($p = 0.04$) and head circumference ($p = 0.01$) after adjusting for potential confounders [3]. The combination of high DNA adducts and ETS exposure was associated with 233 g (7%) reduction of birth weight and 1 cm (3%) reduction of head circumference. Those results suggest that the effect of ETS may be due to other, non-PAH, constituents of tobacco and that adducts may largely reflect other environmental sources of PAH as well as individual susceptibility to them [3,4]. The postulated mechanisms of the foetal toxicity of PAH may involve the induction of apoptosis after DNA damage from PAH, antiestrogenic effects of PAH, binding to the human aryl hydrocarbon receptor to induce P450 enzymes or to receptors for placental growth factors which can result in decreased exchange of oxygen and nutrients [5,7].

In the Czech Republic, ambient PAH exposure in early stage of pregnancy significantly increased the risk of intrauterine growth retardation (IUGR) [5]. Using a continuous measure of exposure, a 10ng/m^3 increase in carcinogenic fraction of PAH in the first gestational month was associated with increased risk of IUGR (adjusted OR 1.22; 95% Cl = 1.07–1.39).

The series of analysis of the relationship between in utero exposure to airborne PAH and foetal growth were performed in two parallel prospective studies in New York City (NYC), USA and in Kraków, Poland [2,7–11]. In those studies, study design (prospective cohort studies), eligibility criteria (nonsmoking, healthy, nonoccupationally exposed women, umbilical cord blood cotinine concentrations < 25 ng/ml) and personal air monitoring methodology (48-hr personal air monitoring) were identical. The analysis published in 2003 indicated the statistically significant association between high prenatal exposure to PAH and lower birth weight as well as smaller head circumference [2]. Prenatal PAH exposure was 10-fold higher in Kraków than in NYC and such exposure was associated with significantly reduced birth weight in Kraków and in NYC African Americans ($p < 0.01$) but not in NYC Dominicans. Within the lower exposure range, the effect per unit PAH exposure on birth weight was 6-fold greater for NYC African Americans than for Kraków citizens [7]. Additional analysis performed on African-Americans and Dominicans residing in NYC indicated that 1-ln-unit increase in prenatal PAH exposure was associated with a 2-fold increase in risk of symmetric intrauterine growth restriction, 5-fold increase in risk of preterm delivery and 0.04% increase in cephalisation index in African Americans (after adjusting for potential confounders) [9]. Those effects were also not observed in Dominicans which, as postulated by the authors, might reflect reduction of the risk by healthy lifestyle of this ethnic group.

Several methodological issues should be considered when analysing the impact of PAH exposure on pregnancy outcome. In some studies the important issue is the exposure misclassification, resulting from reliance on routine ambient air monitoring data to approximate personal exposure, or retrospective and cross-sectional study design. Additional problem is that the studies analyse the mutually correlated air pollutants together and it is impossible to separate them and judge which air pollutant is causally associated with birth outcomes. Very important problem when analysing the impact of PAH on pregnancy outcomes are the confounding variables among which smoking as a significant source of PAH seems to be crucial. Additional factors which need to be considered are: sex of newborn, marital status, maternal educational level, maternal prepregnancy body mass index (BMI), weight gain, ETS exposure during pregnancy and medical complications.

The aim of the study was to examine the impact of PAH on foetal growth including: birth weight (BW), length,

head (HC) and chest (CHC) circumference, ponderal (PI) and cephalisation indices (CI).

The advantage of our analysis is the prospective study design which enables reliable assessment of individual exposure to the PAH in second trimester of pregnancy. The analysis of 1-hydroxypyrene (1-HP) in urine collected in the second trimester of pregnancy enables identification of all sources of exposures to PAH. The active and passive smoking was verified by cotinine level in saliva collected three times in pregnancy and the information about other potential confounding factors was updated throughout the pregnancy period.

MATERIAL AND METHODS

Study design and sample

The analysis used the data from the prospective Polish Mother and Child Cohort Study. The complete description of the cohort was published elsewhere [13]. Briefly, the study was performed in 8 regions of Poland. The recruitment and all scheduled visits were conducted in selected maternity units or clinics of the study districts. The study population included in this analysis consisted of 449 mother-child pairs.

We included into the study women between 8–12 weeks of single pregnancy, not assisted with reproductive technology, and not expected to be finished as spontaneous abortion. All women with the serious chronic diseases specified in study protocol were excluded from the study.

Questionnaires

All women participating in the study were interviewed three times during pregnancy (once in each trimester). The information collected by questionnaires were focused on socio-demographic characteristic, previous and current pregnancies, lifestyle exposures including active and passive smoking, alcohol consumption and food frequency questionnaire. After delivery, a detailed questionnaire was filled by gynaecologist and neonatologist describing mode of delivery and newborn condition including gestational age, birth weight, length, head and chest circumference.

Exposure variables

Exposure to PAH

Concentration of 1-HP in urine sample was chosen as the biomarker of exposure to PAH. The urine sample was collected from the women between 20–24 weeks of pregnancy. The 1-HP was analysed using high performance liquid chromatography (HPLC).

Exposure to active and passive smoking

The active and passive smoking exposure was verified by salivary level of cotinine, the major metabolite of nicotine. Saliva was collected three times in pregnancy (once in each trimester). The analytical measurement was performed using high performance liquid chromatography coupled with tandem mass spectrometry/positive electrospray ionisation ($LC\text{-}ESI^{+}MS/MS$) and isotope dilution method. This procedure has been validated under ISO 17025 criteria and accredited by Polish Center of Accreditation (Certificate AB215). All women for whom cotinine level in saliva was higher than 10 ng/ml were classified as smokers.

Outcome variables

The analysis was performed for child birth weight (g), length (cm), head and chest circumference (cm). Additionally ponderal (PI) and cephalisation (CI) indices were calculated. PI, an indicator for thinness of the newborn, was calculated as the ratio of the BW (g) / length^3 (cm^3) X 100 [9,14]. CI was defined as HC (cm) / BW (g)$\times$10 000 [9,15–16]. For those variables the mean, median range and interquartile range (IQR) was calculated. IQR, a measure of statistical dispersion, is equal to the difference between the third and first quartiles.

Confounding variables

Independent risk factors and confounders identified from the literature were included in the analysis. First analysis was performed with the adjustment for gender of newborn and gestational age. The additional variables included in the model were: marital status, maternal educational level, season of last menstruation period (LMP), maternal prepregnancy BMI and maternal weight gain in pregnancy.

As the tobacco smoking and ETS are the important sources of PAH exposure, the analysis between 1-HP in urine and outcome variables was additionally adjusted for cotinine level in saliva.

Statistical analysis

To determine the pregnancy outcomes related to PAH exposure, the multivariate analyses were conducted using the linear regression model. Three sets of potential confounders were considered. A square root transformation was used for 1-HP concentration. Statistical inference was based on two-sided tests at 0.05 significance level. R software, version 10.1, was used for the statistical analysis.

RESULTS

Pregnant women demographic characteristic and newborn anthropometric indicators

Socio-demographic characteristics of the study population are presented in Table 1. Most of the pregnant women included in the study were in the age category 20–30 years (70%) and 27% of them were older than 30. More than half of the subjects lived in big cities (500 000 of inhabitants) and 19% of them in cities with 100 000–500 000 of inhabitants and the same percentages in smaller ones (< 10 000 of inhabitants). About 74% of the women were married. About 56% of women had no children, 37% of them had one child and 5% had two. More than half of the study population had 12 or more years of education and 34% of them had 9–12 years of education. About 20% of the women had saliva cotinine level higher than 10 ng/ml which, according to our criteria, indicated that they were tobacco smokers. Ten percent of the women had prepregnancy BMI indicating that they were overweight (BMI = 25–30 kg/m^2) and 5% that they were obese (BMI ≥ 30 kg/m^2). For most of the women weight gain during pregnancy was between 10 and 20 kg, for 8% of them it was higher than 20 kg and for 2.4% it was less than 5 kg. In 74% of women, as indicated by last menstruation period, the child was conceived during the summer or fall season.

Table 1. Socio-demographic characteristics of the study population

Characteristic	Study population (N = 449)	
	n	%
Age (years)		
≤ 20	16	3.6
20–30	313	69.7
≥ 31	120	26.7
Marital status		
married	333	74.2
divorced	12	2.7
single	104	23.2
Number of children		
0	253	56.3
1	167	37.2
2	24	5.4
> 2	5	1.1
Maternal education (years)		
< 9	59	13.1
9–12	153	34.1
≥ 12	237	52.8
Employment status		
unemployed	67	14.9
employed	382	85.1
Place of residence (number of inhabitants in thousands)		
> 500	254	56.6
100–500	86	19.2
10–100	17	3.8
< 10	92	20.5
Cotinine level		
≤ 10 ng/ml	360	80.2
> 10 ng/ml	89	19.8
Prepregnancy BMI (kg/m^2)		
< 20	130	29.0
20–24.9	252	56.1
25–29.9	47	10.5
≥ 30	20	4.5
Maternal weight gain during pregnancy (kg)		
< 5	11	2.4
5–10	88	19.6
10–20	314	69.9
> 20	36	8.0
Season of LMP		
summer (Jun–Aug)	144	32.1
fall (Sep–Nov)	189	42.1
winter (Dec–Feb)	57	12.7
spring (Mar–May)	59	13.1

The mean 1-HP concentration in the urine of women participating in the study was 0.37 μg/g creatinine with the range 0.03–10.2 μg/g creatinine.

Table 2 presents the newborn anthropometric indicators. The mean child birth weight was 3371 g and the range was 1780–4800 g. The child length was between 45 and 63 cm with the mean length 55 cm. The mean newborn head and chest circumferences were 34 cm (range: 27–39 cm). Additionally the ponderal and cephalisation indices were calculated.

Association between 1-HP in urine and child parameters at birth

Three kind of analysis with the incursion of different confounding factors were performed (Table 3). The exposure to PAH significantly decreased child birth weight ($\beta = -245.6$; $p < 0.001$), length ($\beta = -1.2$; $p = 0.001$), head and chest circumference ($\beta = -0.7$; $p = 0.006$ and $\beta = -0.8$; $p = 0.001$) after adjustment for child gender and gestational age. PAH exposure was not associated with significant reduction in ponderal index ($\beta = -0.02$; $p = 0.5$). On the other hand, 1-sqrt unit exposure to PAH increase was associated with 0.06% increase in cephalisation index. The second analysis performed with the adjustment for additional factors, including pregnant women marital status, educational level, season of LMP, prepregnancy BMI, and weight gain in pregnancy confirmed the significant association between PAH exposure and child birth weight ($\beta = -158.3$; $p = 0.01$), chest circumference ($\beta = -0.7$; $p = 0.02$) and CI ($\beta = 4.2$; $p = 0.01$). However, when the cotinine level in saliva — the biomarker of active and passive smoking had been included in the analysis, all the results were not statistically significant ($p > 0.05$).

Table 2. Newborn anthropometric indicators

Characteristic	Median	Mean	IQR (25–75%)	Range	Missing values
Birth weight (g)	3 380.00	3 371.00	3 055.00–3 660.00	1 780.00–4 800.00	26
Child length (cm)	55.00	55.00	53.00–57.00	45.00–63.00	30
Head circumference (cm)	34.00	34.00	33.00–35.00	27.00–39.00	32
Chest circumference (cm)	34.00	34.00	32.00–34.00	27.00–39.00	35
Ponderal index (g/cm^3)	2.00	2.02	1.89–2.15	1.27–2.75	30
Cephalisation index (cm/g)	102.30	103.30	94.40–109.70	74.40–168.50	32

IQR — Interquartile range.

Table 3. Association between 1-HP in urine and child parameters at birth

Outcome	Adjusted*			Adjusted**			Adjusted ***		
	coef.	se	p	coef.	se	p	coef.	se	p
Birth weight (g)	–245.60	64.50	< 0.001	–158.30	64.600	0.01	–105.400	66.100	0.10
Child length (cm)	–1.20	0.40	0.001	–0.70	0.400	0.05	–0.400	0.400	0.30
Head circumference (cm)	–0.70	0.20	0.006	–0.50	0.300	0.05	–0.300	0.300	0.20
Chest circumference (cm)	–0.80	0.30	0.001	–0.70	0.009	0.02	–0.400	0.300	0.07
Ponderal index (g/cm^3)	–0.02	0.03	0.500	–0.02	0.030	0.60	–0.003	0.003	0.40
Cephalisation index (cm/g)	6.30	1.70	< 0.001	4.20	1.700	0.01	3.000	1.700	0.09

* For gestational age, gender of the newborn.

** For gestational age, gender, marital status, educational level, season of LMP, prepregnancy BMI, weight gain in pregnancy.

*** For gestational age, gender, marital status, educational level, season of LMP, prepregnancy BMI, weight gain in pregnancy and cotinine level in saliva.

The additional analysis was preformed among the group of women whose salivary cotinine levels were below 10 ng/ml (360 women) with the adjustment for potential confounding factors (child gender, gestational age, marital status, educational level, season of LMP, prepregnancy BMI, weight gain in pregnancy). Based on this analysis, the exposure to PAH was not significantly associated with child parameters at birth ($p > 0.05$).

DISCUSSION

In the present study, the exposure to PAH measured by 1-HP level in urine of pregnant women was significantly associated with child birth weight ($\beta = –158.3$; $p = 0.01$), chest circumference ($\beta = –0.7$; $p = 0.02$) and cephalisation index ($\beta = 4.2$; $p = 0.01$) after adjustment for gestational age, child gender pregnant women marital status, educational level, season of LMP, prepregnancy BMI and weight gain in pregnancy. After inclusion in the analysis the salivary cotinine level, a biomarker of tobacco smoking and ETS exposure, the results were not statistically significant.

By conducting prospective cohort study and measuring 1-HP in urine of women participating in the study, we have addressed some of the limitations in the studies analysing the association between PAH exposure and birth parameters, such as misclassification bias and retrospective or cross-sectional exposure assessment.

Most studies are evaluating the exposure to airborne PAH based on PAH-DNA adducts or personal air monitoring. In our study, the exposure assessment based on 1-HP level in urine enabled analysing of several exposure sources (i.e. air pollution, smoking and diet) [1–3,9–11]. The measurement of PAH-DNA seems to be reasonable when the airborne sources of PAH predominate, whereas measuring 1-HP in urine in case of low level of the exposure to airborne PAH is more appropriate for evaluation of other sources of PAH.

Other studies have previously observed an association between PAH exposure and birth outcomes such as birth weight, child length, head and chest circumference and ratio of head circumference to birth weight [1–11]. Most of the studies focused in analysis on the known possible confounding variables, including child gender, pregnant women marital status, educational level, season of delivery, prepregnancy BMI and weight gain in pregnancy, which were also addressed in our analysis. Additionally we have been able to eliminate one of the most important confounders by restricting our cohort to healthy women with no serious pregnancy complications or known risk of adverse birth outcomes. Tobacco smoking has been a major source of PAH. In most studies, the study population was restricted to nonsmokers. In some of them the inclusion criteria were based on information from mothers about their smoking status, which lead to misclassification bias. Additionally, some studies analyse the umbilical cord blood cotinine level to verify smoking status or ETS exposure.

In our study, the smoking status was verified by determination of salivary cotinine level three times during pregnancy. This enables reliable verification of smoking status and ETS exposure and noting of any changes in smoking status. After the salivary cotinine levels had been included in the analysis, our results did not show any statistically significant association between PAH and birth outcomes. The impact of PAH on pregnancy parameters observed without the inclusion of cotinine level as the confounding factor can be explained in a few ways. The tobacco smoking might be the most important source of PAH exposure and without that factor the level of PAH exposure is not a significant health factor. Our previous analysis conducted on the pregnant women indicated that the mean concentration of 1-HP in urine of nonsmoking woman was 0.60 μg/g creatinine, whereas in smoking ones the respective value was 1.35 μg/g creatinine, and among the women with salivary cotinine level higher than 10 ng/ml, the mean concentration of 1-HP in urine was over twofold higher than that in women with cotinine level lower than 10 ng/ml after adjustment for the day of urine sample collection (ratio of geometric mean 2.3; 95% CI = 1.7–3.0) [17]. This confirmed that PAH level is strongly correlated with tobacco smoking. It is also confirmed by other studies indicating that 1-HP level in urine in nonsmoking people not occupationally exposed to PAH was below 1 μg/g creati-

nine [18–19]. The second explanation for the lack of the association between PAH and birth outcomes in non-smoking women can be due to other smoking compounds such as nicotine or CO, while 1-HP is merely a surrogate indicator.

CONCLUSION

Prenatal exposure to PAH adversely influences foetal development, including child weight, length, head and chest circumference. Tobacco smoking is a major source of PAH. After controlling for active and passive smoking, the observed associations were not statistically significant.

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