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Impact of Pregnancy on the Levels of Selected Polycyclic Aromatic Hydrocarbons

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Abstract

Objective: To compare the levels of selected polycyclic aromatic hydrocarbons (PAH) between pregnant and non-pregnant females.

Design: Cross-sectional for pregnant and non-pregnant females who participated in National Health and Nutrition Examination Survey (NHANES) for the years 2001-2010 were examined. Data for 10 urinary metabolites of PAH, namely, 1-hydroxynaphtahlene, 2-hydroxynaphtahlene, 2-hydroxyfluorene, 3-hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 4-hydroxyphenanthrene and 1-hydroxypyrene were analyzed.

SettingCross-sectional data for pregnant and non-pregnant females from NHANES for the year 2001-2010.

Subjects: The study sample included 334 pregnant and 1679 non-pregnant females aged 20-44 years who participated in NHANES for the period 2001-2010.

Results: Pregnant females had statistically significantly lower levels of 2-hydroxyfluorene (394.4 *vs.* 457.1 ng/L, p=0.03), 3-hydroxyfluorene (139.1 *vs.* 207.9 ng/L, p<0.01), and 3-hydroxyphenanthrene (87.9 *vs.* 109.6 ng/L, p<0.01) than non-pregnant females but statistically significantly higher levels of 1-hydroxyphenanthrene (185.3 *vs.* 133.8 ng/L, p<0.01), 4-hydroxyphenanthrene (47.3 *vs.* 37.9 ng/L, p<0.01) and 1-hydroxypyrene (155.2 *vs.* 126.7 ng/L, p=0.04). Smokers had statistically significantly higher levels for every PAH metabolite than non-smokers (p<0.01), for example, for 1-hydroxynaphthalene, adjusted levels for smokers and nonsmokers were 9329.0 *vs.* 3277.5 ng/L (p<0.01) and for 2-hydroxynaphthalene, adjusted levels for smokers and nonsmokers were 7551.8 *vs.* 1231.2 ng/L (p<0.01). Observed levels of all 10 PAH metabolites increased (p<0.01) over 2001-2010 for both pregnant and non-pregnant females.

Conclusion: Depending up on the individual PAHs, pregnancy may accelerate or decelerate excretion of PAH metabolites.

Keywords: Birth outcomes; Polycyclic aromatic hydrocarbons; Pregnancy; Smoking; Teratogens

Introduction

Polycyclic aromatic hydrocarbons (PAHs), a group of more than 100 chemicals, are usually produced during incomplete combustion of organic materials. Organ systems affected by exposure to PAHs include dermal, hepatic and immunologic [1]. Smoking, grilling, broiling, or other high temperature processing can result in the formation of PAHs. The emitted PAHs can form or bind to particles in the air, and particle size depends in part on the source of the PAH [2]. Relatively higher concentrations of PAHs are associated with smaller particulates [2,3] Uncooked foods and vegetables generally contain low levels of PAHs but can be contaminated by airborne particle deposition [4]. Among pregnant females, higher levels of PAHs have been reported to be associated with usage of coal for residential heating [5], living near coal-fired power plant [6], and exclusively cooking with wood or kerosene than with liquefied petroleum gas or coal briquette [7].

Impact of exposure to PAHs during pregnancy on birth outcomes have been evaluated by several authors in several different birth cohorts [8-11] Maternal exposure to PAHs was found to be associated with (i) decreased birthweight [12-16], (ii) decreased chest circumference and increased cephalization index [13,17], (iii) decreased height of 1.1 cm at age of 3 years for PAHs levels above 34.7 ng/m^3 [18] (iv) small for gestational age birth [17,19], (v) preterm birth [20], (vi) decreased lung function among non-asthmatic children of nonsmoking mothers [21] (vii) depressed verbal IQ [22,23], (viii) adverse neurodevelopmental consequences [24-27], (ix) increased risk of neuroblastoma [28,29] and neural tube defects [30], (x) increased risk of obesity [31], and (xi) increased risk of acute lymphoblastic leukemia [29]. Occupational exposure among mothers aged ≥ 20 years was reported to be associated with gastroschisis (Odds Ratio: 2.53) among children born to them [32] suggesting that exposure to PAHs may be teratogenic. Maternal exposure to PAHs was also shown to be associated with increased risk of offspring being born with a cleft of lip with or without a cleft of palate [33].

The role of mainstream as well as environmental tobacco smoke (ETS) in combination with exposure to PAHs among pregnant females has been studied by several authors. Higher levels of selected PAHs among pregnant smokers have been reported [34,35] Combined effect of exposure to PAHs and ETS among pregnant females has been reported to adversely affect fetal development [6,36-39].

To the best of our knowledge, we do not know of a study that has evaluated the impact of pregnancy on the levels of PAHs using a nationally representative sample of females. Thus, this study was undertaken to evaluate the degree to which pregnancy may affect the urinary levels of selected PAH metabolites among females aged 20-44 years old. Data from National Health and Nutrition Examination Survey [40] for the years 2001-2010 were selected to be used for this purpose.

Materials and Methods

Data source and data description

Data from NHANES [40] for the years 2001-2010 from demographic, PAH metabolites, body measures, serum cotinine, urine creatinine, serum ferritin, and pregnancy as determined by urine pregnancy tests [41] were downloaded and match merged. The sampling plan for NHANES is a complex, stratified, multistage, probability cluster designed to be representative of the civilian, non-institutionalized U.S. population. For PAHs, data for ten metabolites were available in urine samples, namely, 1-hydroxynaphtahlene (NAP1), 2-hydroxynaphtahlene (NAP2), 2-hydroxyfluorene (FLU2), 3-hydroxyfluorene (FLU3), 9- hydroxyfluorene (FLU9), 1-hydroxyphenanthrene (PHE1), 2-hydroxyphenanthrene (PHE2), 3-hydroxyphenanthrene (PHE3), 4-hydroxyphenanthrene (PHE4), and 1-hydroxypyrene (PYE1). Data for NAP1, NAP2, FLU2, FLU3, PHE1, PHE2, PHE3, and PYE1 were available for all five NHANES cycles included in the study. However, data for FLU9 were not available for 2001-2002 and data for PHE4 were available for 2003-2006 only. Percent observations below the limit of detection (LOD) for all ten metabolites were above 95%. All values below the limit of detection were imputed as LOD/√2.

A total of 2013 participants were available for analysis. Details are given in Table 1.

		Overall			
		Pregnant		**Non-pregnant**	
		N	Percentage (%)	N	Percentage (%)
Total		334	100	1679	100
Race/Ethnicity	Non-Hispanic White	151	45.2	735	43.8
	Non-Hispanic Black	43	12.9	351	20.9
	Mexican American	99	29.6	360	21.4
	Others	41	12.3	233	13.9
Smoking status	Nonsmoker	279	83.5	1177	70.1
	Smoker	31	9.3	419	25
	Missing	24	7.2	83	4.9
Iron storage status*	Iron absent	123	36.8	314	18.7
	Iron deficient	69	20.7	255	15.2
	Iron replete	118	35.3	1026	61.1
	Missing	24	7.2	84	5
NHANES year	2001-2002	99	29.6	318	18.9
	2003-2004	76	22.8	303	18
	2005-2006	113	33.8	285	17
	2007-2008	20	6	360	21.4
	2009-2010	26	7.8	413	24.6

Table 1: Un-weighted sample sizes by race/ethnicity, smoking and iron storage statuses, pregnancy trimester, and survey year for pregnant and no pregnant females aged 20-44 years. Data from National Health and Nutrition Examination Survey 2001-2010.

Laboratory methods used to detect and measure various PAH metabolites for the years 2007-2008 are available elsewhere [42] and similar files for all other years. Of the 2013 females aged 20-44 years analyzed for this study, 334 were pregnant as determined by a urine

pregnancy test and 1679 were non-pregnant. Of the 334 pregnant females, 51 self-reported to be in the first trimester of their pregnancies, 117 self-reported to be in the second trimester of their pregnancies, 155 self-reported to be in the third of their pregnancies, and, for 51 pregnant females data on duration of their pregnancies were missing. However, since longitudinal data on variability in the levels of PAHs over total pregnancy were not available, it was not considered to be meaningful to study variability in PAH levels during the course of pregnancy.

Outcome variables

Log10 transformed values of each of the ten PAH metabolites were the outcome variables and as such were used as dependent variables in regression models.

Covariates

The independent variables/covariates considered for regression modeling were: age as a continuous variable, pregnancy status (pregnant, non-pregnant) as determined by a urine pregnancy test, race/ethnicity (non-Hispanic white or NHW, non-Hispanic black or NHB, Mexican Americans or MA, other unclassified race/ethnicities or OTH), iron storage status (absent, deficient, replete) smoking status (nonsmoker, smoker), body mass index (BMI), NHANES survey year, urine creatinine, and fasting time before the urine samples were collected. Family poverty income ratio (PIR) was used as a surrogate variable for socioeconomic status. Iron storage status was defined as being absent if the values of serum ferritin were <16.5 ng/ml. Those, with serum ferritin values between 16.5 and 26.5 ng/mll were defined as being iron deficient and those with >26.5 ng/ml as iron replete. This classification has been used by Jain [43] among others. Smokers were defined as those with serum cotinine values ≥ 10 ng/ml and nonsmokers were defined as those with serum cotinine values <10 ng/ml. Jain [43] also defined smoking status using these cut offs.

A consideration was given to use consumption of broiled/smoked meat/fish as an independent variable. An attempt was made to identify those participants from the 24-hour recall dietary databases for NHANES years 2005-2006 [44] and other years that specifically were reported to have eaten broiled and/or smoked food items. However, it was not always possible to determine if the food that was eaten was broiled or baked. For example, for the United States Department of Agricultural (USDA) food code database, the description provided in the NHANES 24-hour recall dietary database for USDA food code 21101120 was "BEEF STEAK, BROILED OR BAKED, LEAN and FAT". In such instances, it was not possible to determine if the food was baked or broiled. Since non-availability of complete data did not allow creation of a variable representing consumption of broiled/smoked food, consumption of broiled/smoked food was not included in the analyses as an independent variable. This is a limitation of the study.

Statistical analysis

All data were analyzed using SAS 9.3 (www.sas.com). SAS Proc SURVEYREG was used to fit regression models. Two way interactions between smoking status, pregnancy status, iron storage status, and race/ethnicity were included in preliminary models but were included in the final models if one or more of them were found to be statistically significant at α=0.05.

Multivariate analysis

First of all, two way interactions between race/ethnicity, pregnancy status, smoking status, and iron storage status were tested for statistically significant differences by fitting regression models with log10 transformed values of PAH metabolites as dependent variable and covariates as listed in Section 2.3 as independent variables. Once, statistically significant interactions for each of the ten PAH metabolites have been identified, regression models were fitted for each of the ten PAH metabolites to (i) compute adjusted geometric means (AGM) by race/ethnicity, pregnancy status, smoking status, and iron storage status as well as interaction terms, if any in the model, with 95% confidence intervals, (ii) test for statistically significant differences between AGMs using t-test, (iii) estimate regression slopes with p-values for each of the continuous independent variable as listed in Section 2.3.

Results

Data for AGMs by race/ethnicity, smoking status, pregnancy status, and iron storage status are given in (Table 2). Data for statistically significant interactions between race/ethnicity and smoking status for NAP2 (Table 3); between smoking status and iron storage status for NAP2 and PHE4 (Table 4); between pregnancy and iron storage status for FLU9, PHE1, PHE2, and PHE4, and PYE1 (Table 5), and pregnancy and smoking status for FLU9 (Table 6) are also provided.

	NAP1[1]	NAP2[2]	FLU2[3]	FLU3[4]	FLU9[5]
Non-Hispanic White (NHW)	3358.8 (2971.4-3796.6)	5600.7 (4943.5-6345.2)	471.6 (435.2-511.2)	182.1 (166.8-198.9)	374.1 (338.1-413.8)
Non-Hispanic Black (NHB)	2860 (2325.1-3518)	4812.5 (4045.5-5724.8)	409.8 (360.7-465.6)	183 (161.8-207)	329.3 (283.4-382.6)
Mexican American (MA)	2887.7 (2354.8-3541.2)	6440.6 (5430.3-7639)	425.9 (386.7-469)	156.3 (139.9-174.7)	358.5 (314.2-409)
Others (OTH)	3116.2 (2514.2-3862.4)	5385.4 (4422.4-6558)	394.8 (347.8-448.3)	160.5 (139.8-184.4)	301.2 (256.9-353.3)
Pregnant (P)	2813.8 (2175-3640.2)	5475.2 (4626.3-6479.9)	394.4 (350.4 -443.9)	139.1 (120.8-160.2)	341.1 (290.1-401.1)
Non-pregnant (NP)	3304.2 (2969.9-3676.2)	5584.4 (5147.7-6058.1)	457.1 (427.6 -488.6)	207.9 (193.6-223.2)	338.1 (309.1-369.8)
Non-Smokers (NSM)	1231.2 (1080.3-1403.1)	3277.5 (2950.5-3640.8)	183.3 (170.9 -196.6)	58.6 (54.5-63.1)	250.7 (226.2-277.8)
Smokers (SM)	7551.8 (6299.9-9052.5)	9329 (8012.3-10862)	983.5 (879.9-1099.2)	493.3 (435.4-559)	460.1 (403.1-525.1)

Iron Absent (IA)	2990.9 (2530.4-3535.2)	5853.6 (5090.5-6731.2)	438.9 (397.2-485)	174 (155.2-195)	404.7 (344.2-475.9)
Iron Deficient (ID)	3071.1 (2503.9-3766.8)	5535.2 (4739.6-6464.4)	432.2 (384-486.4)	177.5 (156.4-201.5)	335.2 (274.5-409.3)
Iron Replete (IR)	3086.4 (2636.9-3612.5)	5218 (4696-5798)	403.6 (372.6-437.1)	159.3 (145.1-174.8)	288.7 (263.7-316)
	PHE1[6]	**PHE2**[7]	**PHE3**[8]	**PHE4**[9]	**PYE1**[10]
Non-Hispanic White (NHW)	195.3 (180-212)	79.9 (72-88.7)	107.2 (97.2-118.2)	45 (37.5-54)	137.9 (123-154.6)
Non-Hispanic Black (NHB)	141.1 (125.6-158.6)	66.1 (57.8-75.7)	103 (91.1 -116.5)	39 (31.4-48.5)	137 (120.1-156.3)
Mexican American (MA)	170.1 (149.2-194)	75.8 (65.4-87.9)	91 (80.4-102.9)	45.6 (36.3-57.3)	147.6 (129.1-168.8)
Others (OTH)	162.5 (144.2-183.1)	74.4 (66.3-83.5)	92.5 (81-105.6)	40.1 (33.2-48.4)	138.7 (123.1-156.3)
Pregnant (P)	185.3 (161.3-213)	78.8 (68.1-91.3)	87.9 (75.4-102.5)	47.3 (38-58.8)	155.2 (130.3-184.8)
Non-pregnant (NP)	148.9 (140-158.4)	69.3 (64.9-73.9)	109.6 (103.4-116.2)	37.9 (32-44.9)	126.7 (118.8-135.2)
Non-smokers (NSM)	133.8 (123.8-144.6)	54.6 (49.8-60)	63.8 (58.6-69.4)	28.1 (24.4-32.4)	89.1 (80.5-98.7)
Smokers (SM)	206.2 (184.6-230.5)	99.9 (89.7-111.3)	151.2 (133.5-171.2)	63.7 (50.8-79.9)	220.7 (194.9-250)
Iron Absent (IA)	189.8 (166.8-215.9)	82 (71.3-94.4)	100.5 (89.8-112.5)	48.5 (38.6-61)	162.3 (140.9-186.9)
Iron Deficient (ID)	161.4 (139.5-186.8)	75.5 (66.5-85.9)	96.4 (85.9-108.3)	44 (34.9-55.6)	146.6 (126.7-169.6)
Iron Replete (IR)	149.7 (135.5-165.4)	65.1 (56.4-75.1)	97.6 (88.7-107.5)	35.5 (30.3-41.6)	116 (98.3-136.8)

[*]NAP1=1-hydroxynapthalene, NAP2=2-hydroxynapthalene, FLU2=2-hydroxyfluorene, FLU3=3-hydroxyfluorene, FLU9=9-hydroxyfluorene, PHE1=1-hydroxyphenanthrene, PHE2=2-hydroxyphenanthrene, PHE3=3-hydroxyphenanthrene, PHE4=4-hydroxyphenanthrene, PYE1=1-hydroxypyrene

[1]SM>NSM (p<0.01)

[2]NHW>NHB (p=0.049), NHB<MA (p<0.01), SM>NSM (p<0.01)

[3]NHW>NHB (p=0.02), NHW>OTH (p<0.01), P<NP (p=0.03), SM>NSM (p<0.01)

[4]NHW>MA (p<0.01), NHB>MA (p=0.03), P<NP (p<0.01), SM>NSM (p<0.01)

[5]NHW>OTH (p<0.01), SM>NSM (p<0.01), IA>IR (p<0.01).

[6]NHW>NHB (p<0.01), NHW>MA (p=0.03), NHW>OTH (p<0.01), NHB<MA (p<0.01), P>NP (p<0.01), SM>NSM (p<0.01), IA>IR (p<0.01)

[7]NHW>NHB (p<0.01), SMK>NSM (p<0.01), IA>IR (p=0.02)

[8]NHW>MA (p=0.02), NHW>OTH (p=0.02), P<NP (p<0.01), SM>NSM (p<0.1)

[9]NHW<OTH (p=0.02), NHW>OTH (p=0.02), P>NP (p<0.01), SM>NSM (p<0.01)

[10]P>NP (p=0.04), SM>NSM (p<0.01), IA>IR (p<0.01)

Table 2: Adjusted geometric means with 95% confidence intervals for selected polycyclic aromatic hydrocarbon (PAH)[*] metabolites in ng/L by race/ethnicity, pregnancy and smoking status for females aged 20-44 years. Data from National Health and Nutrition Examination Survey 2001-2010.

Non-Hispanic White Nonsmokers (NHW_NSM)	2572.7 (2243.7-2950)	NHW_SM >NHW_NSM (p<0.01)
Non-Hispanic White Smokers (NHW_SM)	12192.3 (10072.114758.8)	NHW_NSM<MA_NSM (p<0.01)
Non-Hispanic Black Nonsmokers (NHB_NSM)	2980.6 (2584.3-3437.7)	NHW_NSM<OTH_NSM (p<0.01)
Non-Hispanic Black Smokers (NHB_SM)	7770.2 (5818.5-10376.6)	NHW_SM>NHB_SM (p<0.01)
Mexican American Nonsmoker (MA_NSM)	4282.7 (3762.9-4874.3)	NHB_NSM<NHB_SM (p<0.01)
Mexican American Smoker (MA_SM)	9685.8 (7116.7-13182.3)	NHB_NSM<MA_NSM (p<0.01)

Other Nonsmoker (OTH_NSM)	3513.6 (2876.5-4291.8)	OTH_NSM<OTH_SM (p<0.01)
Other Smoker (OTH_SM)	8254.3 (5552-12271.7)	

Table 3: Adjusted geometric means with 95% confidence intervals for 2-hydroxynaphthalene in ng/L by race/ethnicity and smoking status. Data from National Health and Nutrition Examination Survey 2001-2010.

	2-hydroxynaphthalene	**4-hydroyphenanthrene**
Nonsmoker with Iron Absent (NSM_IA)	3124 (2612.7-3735.2)	28.4 (22.5-35.8)
Nonsmoker with Iron Deficient (NSM_ID)	3593.4 (3058.8-4221.4)	32.6 (26.7-39.9)
Nonsmoker with Iron Replete (NSM_IR)	3136.3 (2838.7-3465.1)	24 (20.9-27.6)
Smoker with Iron Absent (SM_IA)	10968.4 (8876.5-13553.3)	83 (61.3-112.3)
Smoker with Iron Deficient (SM_ID)	8526.4 (6623.8-10975.3)	59.5 (39.4-89.9)
Smoker with Iron Replete (SM_IR)	8681.5 (7381.6-10210.2)	52.4 (40.3-68.2)
Statistically Significant Differences	SM_IA>NSM_IA (p<0.01)	SM_IA>NSM_IA (p<0.01)
	SM_ID>NSM > ID (p<0.01)	NSM_ID>NSM_IR (p<0.01)
	SM_IR>NSM > IR (p<0.01)	NSM_ID<SM_ID (p=0.01)
	SM_ID<SM_IR (p=0.03)	NSM_IR<SM_IR (p<0.01)

Table 4: Adjusted geometric means with 95% confidence intervals in ng/L for 2-hydroxynaphthalene and 4-hydroxyphenanthrene. Data from National Health and Nutrition Examination Survey 2001-2010.

	9-hydroxyfluorene	**1-hydroxyphenanthrene**	**2-hydroxyphenanthrene**	**4-hydroxyphenanthrene**	**1-hydroxypyrene**
Pregnant with Iron Absent (P_IA)	485 (371.6-633.1)	240 (187.8-306.8)	100 (77.8-128.5)	65.1 (45.4-93.3)	213.6 (160.5-284.2)
Pregnant with Iron Deficient (P_ID)	323.1 (214.7-486)	182.6 (139.1-239.8)	80.9 (63.3-103.3)	46.6 (32.6-66.5)	160.6 (122.7-210.1)
Pregnant with Iron Replete (P_IR)	253.3 (213.6 -300.3)	145.2 (120.5-175.1)	60.6 (46.2-79.5)	34.8 (27.2-44.6)	109 (78.7-150.9)
Non-Pregnant with Iron Absent (NP_IA)	337.7 (290.2-393.1)	150.1 (136.4-165.1)	67.3 (60.4-75)	36.2 (28.2-46.3)	123.3 (110.8-137.2)
Non-Pregnant with Iron Deficient (NP_ID)	347.8 (304.8-396.9)	142.7 (127.3-159.8)	70.6 (63.7-78.1)	41.7 (32-54.2)	133.8 (119-150.4)
Non-Pregnant with Iron Replete (NP_IR)	329 (300.6-360.1)	154.3 (144.7-164.6)	70 (65-75.3)	36.2 (30.5-42.9)	123.4 (114.5-133.1)
Statistically Significant Differences	P_IA>P_IR (p=0.01)	P_IA>P_IR (p<0.01)	P_IA>P_IR(p<0.01)	P_IA>P_IR (p<0.01)	P_IA>P_IR (p<0.01)
	P_IA>NP_IA (p=0.01)	P_IA>NP_IA (p<0.01)	P_IA>NP_IA (p<0.01)	P_IA>NP_IA (p<0.01)	P_IA>NP_IA (p<0.01)
	P_IR<NP_IR (p=0.01)				

Table 5: Adjusted geometric means with 95% confidence intervals in ng/L for 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 4-hydroxyphenenathrene, and 1-hydroxypyrene by pregnancy by iron storage status. Data from National Health and Nutrition Examination Survey 2001-2010.

	9-hydroxyfluorene	**Statistically significant differences**
Pregnant Nonsmokers (P_NSM)	291.1 (238.6-355.1)	P_NSM<P_SM (p=0.03)
Pregnant Smokers (P_SM)	399.7 (317.7-502.8)	P_NSM>NP_NSM (p<0.01)

Non-Pregnant Nonsmokers (NP_NSM)	215.9 (199.2-234)	P_SM<NP_SM (p=0.04)
Non-Pregnant Smokers (NP_SM)	529.5 (465.4-602.5)	NP_NSM<NP_SM (p<0.01)

Table 6: Adjusted geometric means with 95% confidence intervals in ng/L for 9-hydroxyfluorene by pregnancy by smoking status. Data from National Health and Nutrition Examination Survey 2001-2010.

Variability by pregnancy status, smoking status and race/ethnicity

Pregnant females had lower adjusted levels than non-pregnant females for FLU2 (p=0.03), FLU3 (p<0.01), and PHE3 (Table 2, p<0.01). On the other hand, pregnant females had higher adjusted levels of PHE1 (p<0.01), PHE4 (p<0.01), and PYE1 (p=0.04) than non-pregnant females. When interactions between pregnancy and iron storage status was taken into account, the levels of FLU9, PHE1, PHE2, and PHE4, and PYE1 were (i) higher among pregnant females with absent iron than pregnant females with replete iron ($p \leq 0.01$, Table 5), and (ii) higher among pregnant females with absent iron than non-pregnant females with absent iron ($p \leq 0.01$, Table 5). In addition, when interaction between pregnancy and smoking status is taken into account (Table 6), for FLU9, (i) both pregnant and non-pregnant nonsmokers had lower levels (p<=0.03) than pregnant and non-pregnant smokers, (ii) pregnant nonsmokers had higher levels than non-pregnant nonsmokers but non-pregnant smokers had higher levels than pregnant smokers (p<0.01, Table 6).

Smokers had higher adjusted levels of all ten PAH metabolites than nonsmokers (p<0.01, Table 2). Observed levels of certain PAH metabolites for smokers, as compared to nonsmokers, were more than 8-fold higher. For example for FLU3, the observed levels were 58.6 and 493.3 ng/mL (Table 2, p<0.01) for nonsmokers and smokers respectively. For NAP2, smokers had higher levels than nonsmokers irrespective of race/ethnicity but the observed differences between smokers and nonsmokers varied with race/ethnicity (p<0.01, Table 3, 2572.7 *vs.* 12192.3 ng/L for NHW for a difference of 9619.6 ng/L, 2980.6 *vs.* 7770.2 ng/L for NHB for a difference of 4789.6 ng/L, 4282.7 *vs.* 9685.8 ng/L for MA for a difference of 5403.1 ng/L, and 3513.6 *vs.* 8254.3 for OTH for a difference of 4740.7 ng/L). Thus, smoker-non-smoker difference for NAP2 for NHW was almost double of what it is for NHB, MA, and OTH.

NHW had higher adjusted levels than NHB for NAP2 (p=0.049), FLU2 (p=0.02), and PHE1 (p<0.01, Table 2). NHB had higher adjusted levels than MA for FLU3 (p=0.03) but the reverse was true for NAP2 (p<0.01). However, when interaction between race/ethnicity was taken into account, the later difference was applicable for nonsmokers only (Table 3).

Model fit

R2 varied from a low of 43.6% for the model for NAP1 to a high of 71.7% for the model for FLU3 (Table 7). Actual sample sizes used in the model varied from 605 for the model for PHE4 to 1726 for the model for PHE1 (Table 7).

	N	R2	Age	Body mass index	Number of live births	NHANES Cycle	Poverty income ratio	Urine creatinine	Fasting time
			β (p-value)	β (p-value)	β (p-value)	β (p-value)	β (p-value)	β (p-value)	
NAP1	1716	43.6	0.00641 (0.02)	-0.003 (0.32)	-0.00301 (0.78)	-0.01489 (0.17)	-0.01892 (0.07)	0.00324 (<0.01)	-0.00941 (0.01)
NAP2	1723	58.3	0.00485 (0.01)	0.00566 (<0.01)	-0.00312 (0.72)	0.0465 (<0.01)	-0.02533 (<0.01)	0.0037 (<0.01)	-0.00172 (0.4)
FLU2	1723	69.6	0.00522 (<0.01)	0.00506 (<0.01)	-0.0043 (0.51)	-0.01842 (0.01)	-0.02843 (<0.01)	0.00375 (<0.01)	-0.0048 (0.03)
FLU3	1715	71.7	0.00507 (0.01)	0.00103 (0.55)	0.0014 (0.85)	-0.0233 (<0.01)	-0.02431 (<0.01)	0.00351 (<0.01)	-0.00161 (0.46)
FLU9	1363	54.8	0.00391 (0.01)	0.00761 (<0.01)	-0.00964 (0.26)	0.00458 (0.69)	-0.01109 (0.07)	0.00374 (<0.01)	-0.00832 (<0.01)
PHE1	1726	51.8	0.00444 (0.01)	0.00447 (<0.01)	-0.0107 (0.1)	-0.00902 (0.23)	-0.01327 (0.06)	0.00382 (<0.01)	-0.00279 (0.16)
PHE2	1710	50	0.00469 (0.01)	0.00953 (<0.01)	-0.02603 (<0.01)	0.01764 (0.08)	-0.02441 (<0.01)	0.00361 (<0.01)	-0.0064 (<0.01)
PHE3	1718	53.9	0.00495 (<0.01)	0.0006 (0.67)	-0.00938 (0.24)	-0.04047 (<0.01)	-0.01334 (0.03)	0.00355 (<0.01)	-0.00585 (<0.01)
PHE4	605	50.4	0.00459 (0.16)	0.01056 (<0.01)	-0.01439 (0.34)	0.08086 (0.07)	-0.0122 (0.42)	0.00369 (<0.01)	-0.00932 (0.01)
PYE1	1716	58.9	0.00202 (0.3)	0.00204 (0.12)	-0.01597 (0.07)	0.11145 (<0.01)	-0.03155 (<0.01)	0.00369 (<0.01)	-0.00147 (0.52)

*NAP1=1-hydroxynapthalene, NAP2=2-hydroxynapthalene, FLU2=2-hydroxyfluorene, FLU3=3-hydroxyfluorene, FLU9=9-hydroxyfluorene, PHE1=1-hydroxyphenanthrene, PHE2=2-hydroxyphenanthrene, PHE3=3-hydroxyphenanthrene, PHE4=4-hydroxyphenanthrene, PYE1=1-hydroxypyrene

Table 7: Regression slopes for continuous variables with associated p-values for polycyclic aromatic hydrocarbon variables used in the analysis for females aged 20-44 years. Data from National Health and Nutrition Examination Survey 2001-2010.

Association with age, body mass index, number of live births, poverty income ratio, urine creatinine, and fasting time

There was a positive association between age and the adjusted levels of all 10 PAH metabolites except PHE4 and PYE1 (Table 7, $p \leq 0.02$). Adjusted levels of NAP2 (β=0.00566, p<0.01), FLU2 (β=0.00506, p<0.01), FLU9 (β=0.00761, p<0.01), PHE1 (β=0.00447, p<0.01), PHE2 (β=0.00953, p<0.01), and PHE4 (β=0.00459, p<0.01, Table 8) increased with increase in body mass index. There was a decrease in the levels of PHE2 (β=-0.02603, p<0.01) with increase in number of live births (Table 3). Poverty income ratio was negatively associated with the adjusted levels of NAP2 (β=-0.02533, p<0.01), FLU2 (β=-0.02843, p<0.01), FLU3 (β=-0.02431, p<0.01), PHE2 (β=-0.02441, p<0.01), PHE3 (β=-0.01334, p=0.03), and PYE1 (β=-0.03155, p<0.01, Table 7). Urine creatinine was positively associated with the levels of all ten PAH metabolites (p<0.01, Table 7). Fasting time was negatively associated with NAP1 (p=0.01), FLU2 (p=0.03), FLU9 (p<0.01), PHE2, PHE3, and PHE4 ($p \leq 0.01$).

	N	R2	Age	Body Mass Index	Number of Live Births	NHANES Cycle	Poverty Income Ratio	Urine Creatinine	Fasting Time
NAP1	1716	43.6	0.00641 (0.02)	-0.003 (0.32)	-0.00301 (0.78)	-0.01489 (0.17)	-0.01892 (0.07)	0.00324 (<0.01)	-0.00941 (0.01)
NAP2	1723	58.3	0.00485 (0.01)	0.00566 (<0.01)	-0.00312 (0.72)	0.0465 (<0.01)	-0.02533 (<0.01)	0.0037 (<0.01)	-0.00172 (0.4)
FLU2	1723	69.6	0.00522 (<0.01)	0.00506 (<0.01)	-0.0043 (0.51)	-0.01842 (0.01)	-0.02843 (<0.01)	0.00375 (<0.01)	-0.0048 (0.03)
FLU3	1715	71.7	0.00507 (0.01)	0.00103 (0.55)	0.0014 (0.85)	-0.0233 (<0.01)	-0.02431 (<0.01)	0.00351 (<0.01)	-0.00161 (0.46)
FLU9	1363	54.8	0.00391 (0.01)	0.00761 (<0.01)	-0.00964 (0.26)	0.00458 (0.69)	-0.01109 (0.07)	0.00374 (<0.01)	-0.00832 (<0.01)
PHE1	1726	51.8	0.00444 (0.01)	0.00447 (<0.01)	-0.0107 (0.1)	-0.00902 (0.23)	-0.01327 (0.06)	0.00382 (<0.01)	-0.00279 (0.16)
PHE2	1710	50	0.00469 (0.01)	0.00953 (<0.01)	-0.02603 (<0.01)	0.01764 (0.08)	-0.02441 (<0.01)	0.00361 (<0.01)	-0.0064 (<0.01)
PHE3	1718	53.9	0.00495 (<0.01)	0.0006 (0.67)	-0.00938 (0.24)	-0.04047 (<0.01)	-0.01334 (0.03)	0.00355 (<0.01)	-0.00585 (<0.01)
PHE4	605	50.4	0.00459 (0.16)	0.01056 (<0.01)	-0.01439 (0.34)	0.08086 (0.07)	-0.0122 (0.42)	0.00369 (<0.01)	-0.00932 (0.01)
PYE1	1716	58.9	0.00202 (0.3)	0.00204 (0.12)	-0.01597 (0.07)	0.11145 (<0.01)	-0.03155 (<0.01)	0.00369 (<0.01)	-0.00147 (0.52)

*NAP1=1-hydroxynapthalene, NAP2=2-hydroxynapthalene, FLU2=2-hydroxyfluorene, FLU3=3-hydroxyfluorene, FLU9=9-hydroxyfluorene, PHE1=1-hydroxyphenanthrene, PHE2=2-hydroxyphenanthrene, PHE3=3-hydroxyphenanthrene, PHE4=4-hydroxyphenanthrene, PYE1=1-hydroxypyrene

Table 8: Regression slopes for continuous variables with associated p-values for polycyclic aromatic hydrocarbon variables used in the analysis for females aged 20-44 years. Data from National Health and Nutrition Examination Survey 2001-2010.

Time trends

Over the time period 2001-2010, there was an increasing trend in the adjusted levels of NAP2 (β=0.0465, p<0.01) and PYE1 (β=0.11145, p<0.01, Table 7) among females aged 20-44 years of age. However, there was a decreasing trend in the adjusted levels of FLU2 (β=-0.01842, p<0.01), PHE2 (β=-0.0233, p<0.01) and PHE3 (β=-0.04047, p<0.01) over the study period.

Discussion

One of the primary objectives of this study was to evaluate differences between pregnant and non-pregnant females for each of ten PAH metabolites. As described in the next section, pregnancy was associated with higher levels of two PAH metabolites and lower levels of three PAH metabolites.

Impact of pregnancy

During pregnancy, female hormones including different estrogens and progesterone rise steadily until they peak at term. Female hormones at high concentrations influence hepatic drug metabolizing enzyme (DME) expression. Increase in concentrations of both estrogen and progesterone "… can potentially lead to additive, synergistic or antagonistic effects of these hormones on CYP expression" [45]. Expression and activity levels of these DMEs determine clearance of various drugs from the body. This may be the reason why the observed levels of the metabolites of naphthalene and fluorine were lower among pregnant females as compared with non-pregnant females and the observed levels of the metabolites of phenanthrene and pyrene were higher among pregnant females than non-pregnant females. Thus, the observed levels of PAH metabolites among pregnant females exhibit the net effect of modified drug clearance as well as drug transfer to the developing fetus via placenta. As such, even relatively higher drug

levels during pregnancy when compared with non-pregnant state does not rule out the possibility of drug transfer to the developing fetus. At least, based on the statistical significance, levels of FLU2, FLU3, and PHE3 were lower during pregnancy when compared with non-pregnant state which, most likely, translates to the transfer of these metabolites to the developing fetus.

Impact of smoking and race/ethnicity

The fact that smokers had statistically significantly higher levels of each of the ten PAH metabolites than nonsmokers indicates how important it may be for the pregnant females to quit smoking, at least during the pregnancy, in the interest of protecting the developing fetus from harm. The racial/ethnic differences seen in the observed levels of PAH metabolites may be due to differences in how PAHs are metabolized by different race/ethnicities.

Association between PAH levels and age, body mass index, and poverty income ratio

Positive association between age and the adjusted levels of four of the 10 PAH metabolites indicate somewhat higher risk of adverse birth outcomes for relatively older females. During pregnancy, throughout gestation, there is an increase in total body water and adipose tissue resulting in higher body mass index. Positive association between body mass index and the adjusted levels of six of the 10 PAH metabolites indicate higher risk of relatively higher PAH levels among pregnant females when compared non-pregnant females on the average. Poverty income ratio was inversely associated with the levels of six of the 10 PAH metabolites. This implies lifestyles associated with low socioeconomic status have higher risk of exposure to PAHs.

Time trends in the levels of PAHs

When adjusted for other factors that affect PAH levels, the levels of NAP2 and PYE1 increased over the study period of 2001-2010. However, based on unadjusted analysis (data not shown), levels of every PAH metabolite increased over the study period among both pregnant and non-pregnant females. The biennial year increase in the levels of NAP1 ($p<0.01$) and NAP2 ($p<0.01$) among pregnant females were 4.3 ng/L and 5.4 ng/L respectively. These increases for FLU2 ($p<0.01$), FLU3 ($p<0.01$), and FLU9 ($p<0.01$) among pregnant females were 2.4 ng/L, 1.5 ng/L, and 2.2 ng/L every two year respectively. For phenanthrene metabolites also, biennial increases in the levels of PHE1 ($p<0.01$), PHE2 ($p<0.01$), PHE3 ($p<0.01$), and PHE4 ($p<0.01$) were 2.2 ng/L, 1.6 ng/L, 1.6 ng/L, and 1.4 ng/L respectively. Finally, levels of PYE1 increased by 1.9 mg/L ($p<0.01$) every two years. This should be of concern since higher levels of these metabolites are associated with adverse birth outcomes like low birth weight (Table S1).

	Pregnant females		Non-pregnant females	
PAH metabolite*	β (p)	Biennial increase in ng/L	β (p)	Biennial increase in ng/L
NAP1	0.7234 (<0.01)	4.3	0.7464 (<0.01)	4.6
NAP2	0.80467 (<0.01)	5.4	0.80576 (<0.01)	5.4
FLU2	0.52862 (<0.01)	2.4	0.55177 (<0.01)	2.6
FLU3	0.39979 (<0.01)	1.5	0.4641 (<0.01)	1.9
FLU9**	0.50849 (<0.01)	2.2	0.51152 (<0.01)	2.2
PHE1	0.50299 (<0.01)	2.2	0.47941 (<0.01)	2
PHE2	0.40838 (<0.01)	1.6	0.39949 (<0.01)	1.5
PHE3	0.40681 (<0.01)	1.6	0.43303 (<0.01)	1.7
PHE4***	0.38449 (<0.01)	1.4	0.41232 (<0.01)	1.6
PYE1	0.45903 (<0.01)	1.9	0.45377 (<0.01)	1.8
*NAP1=1-hydroxynapthalene, NAP2=2-hydroxynapthalene, FLU2=2-hydroxyfluorene, FLU3=3-hydroxyfluorene, FLU9=9-hydroxyfluorene, PHE1=1-hydroxyphenanthrene, PHE2=2-hydroxyphenanthrene, PHE3=3-hydroxyphenanthrene, PHE4=4-hydroxyphenanthrene, PYE1=1-hydroxypyrene				
**Based on data for 2003-2009				
***Based on data for 2003-2006				

Table S1: Time trends in the levels of selected PAH metabolites over 2001-2010 for pregnant and non-pregnant females aged 20-44 years old. Data from National Health and Nutrition Examination Survey 2001-2010.

Variability in PAH levels across different countries among pregnant females

Polanska et al. [35] found mean PYE1 levels to be 0.4 μ g/g creatinine among pregnant females from a prospective cohort study conducted in 8 regions of Poland. In this study, mean PYE1 levels were found to be 0.09 μg/g creatinine (data not shown) or about 5 times lower than those found in Poland, an observation confirmed by Polanska et al [5]. Personal exposure to PAHs via air has also been reported to be about 10-fold higher in Krakow, Poland as compared to New York City, USA [46]. In a study of Brazilian pregnant females [34], the levels of PYE1 were reported to be 0.02, 0.05, and 0.15 μ mol/mol creatinine for non-smokers, passive smokers, and active smokers.

Limitations of the Study

Limitations of this study dilute the confidence that can be associated with the results obtained from this study. Exposure to PAHs is affected, among many other factors, for example, by the coal used for cooking and heating, food and food processing, vicinity of the place of residence to heavy traffic and housing density, and distance from the place of residence to the main road. The contribution of these factors was not taken into account on exposure levels to PAHs while analyzing data for this study because of non-availability and/or limited availability of data for these factors. It is unknown, in what way, this may have affected the conclusions arrived at in this study. Next, cross-sectional nature of the NHANES data with no knowledge of the timing and ongoing levels of exposure to PAHs generates a level of uncertainty about the value that can be attached with the conclusions arrived at from this study. Only a longitudinal follow up study from pre-pregnancy to post-pregnancy can provide a definitive determination of how the observed levels of PAHs vary from pre-pregnancy to pregnancy period. However, a longitudinal study of the size of NHANES may not be possible for practical and financial reasons.

Summary and Conclusion

In summary, (i) pregnant females had lower levels of FLU2, FLU3, and PHE3 than non-pregnant females, (ii) pregnant females had higher levels of PHE1 and PHE4 than non-pregnant females (iii) smokers had higher levels of every PAH metabolite than non-smokers, and (iv) un-adjusted levels of every PAH metabolite increased over 2001-2010 for pregnant and non-pregnant females.

It is of public health importance to develop educational and other medical/non-medical programs to enable general public to limit exposure to PAHs but these efforts should be made with additional vigor and resources for pregnant females because of the harms the exposures to PAHs can cause to the developing fetus. The harm to the developing fetus is not limited to the adverse birth outcomes like low birth weight, pre-term birth, and others but also the concomitant consequences like neurological deficiencies during early and late childhood. In the opinion of this author, education is the best tool to enable behavioral modifications as long as these programs focus on "what is right" and not "what is wrong and what can go wrong". Consequently, future research efforts to minimize exposures to PAHs among pregnant females should focus on developing educational modules that can advise pregnant females on ways to modify day-to-day behavior (to minimize exposure to PAHs and other environmental contaminants) at home and outside home that is in the best interests of a healthy full-term live birth. Recently developed group prenatal counseling programs called centering pregnancy are very well suited to administer and use such educational modules. In a centering pregnancy prenatal counseling program, eight to twelve females with similar due dates meet regularly with a midwife or doctor trained as a facilitator monthly in the second trimester and every two weeks in the third trimester [47]. Usually, there are 10 counseling sessions each lasting about two hours. Topics discussed during these sessions include breastfeeding, nutrition, and childbirth. These sessions could be very useful for mutual support and sharing individual experiences with other pregnant females. This is the recommendation of this author that these counseling sessions be used to include 20-30 minute educational modules that provide guidance on how to make adjustments in day-to-day behavior that could make it possible to have full-term healthy live births by avoiding exposure to unnecessary environmental contaminants. It may be even more productive if one of the pregnant females in the group administers these modules.

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