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Exposure to Airborne Polycyclic Aromatic Hydrocarbons During Pregnancy and Risk of Preterm Birth

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Abstract

Background—Preterm birth is an important marker of health and has a prevalence of 12-13% in the U.S. Polycyclic aromatic hydrocarbons (PAHs) are a group of organic contaminants that form during the incomplete combustion of hydrocarbons, such as coal, diesel and gasoline. Studies suggest that exposure to PAHs during pregnancy is related to adverse birth outcomes. The aim of this study is to evaluate the association between exposure to PAHs during the pregnancy and preterm birth.

Methods—The study population included births from years 2001-2006 of women whose maternal residence was within 20 km of the primary monitoring site in Fresno, California. Data in the Fresno area were used to form a spatio-temporal model to assign daily exposure to PAHs with 4, 5, or 6 rings at the maternal residence throughout pregnancy of all of the births in the study area. Gestational age at birth and relevant covariates were extracted from the birth certificate.

Results—We found an association between PAHs during the last 6 weeks of pregnancy and birth at 20-27 weeks (OR=2.74; 95% CI: 2.24-3.34) comparing the highest quartile to the lower three. The association was consistent when each quartile was compared to the lowest (OR_{2nd}=1.49, 95% CI: 1.08-2.06; OR_{3rd}=2.63, 95% CI:1.93-3.59; OR_{4th}=3.94, 95% CI:3.03-5.12). Inverse associations were also observed for exposure to PAHs during the entire pregnancy and the first trimester and birth at 28-31 weeks and 20-27 weeks.

Conclusion—An association between PAH exposure during the 6 weeks before delivery and early preterm birth was observed. However, the inverse association with early preterm birth offers an unclear, and potentially complex, inference of these associations.

Keywords

outdoor air pollution; prematurity; polycyclic aromatic hydrocarbons; pregnancy

INTRODUCTION

Preterm birth is an important marker of health in the neonatal period, through childhood and possibly into adulthood. In the U.S., 12-13% of births are preterm (1) – a public health challenge that costs society at least $26 billion a year (2). Preterm birth is generally defined as birth at <37 weeks gestation; however, it can be and should be classified into finer gestational periods. Several studies have examined the relation between air pollution and preterm birth, many of which have found associations with criteria pollutants (monitored by the U.S. Environmental Protection Agency) including particulate matter (PM) with aerodynamic diameter <2.5 and <10 microns ($PM_{2.5}$ and PM_{10}) (3-5).

Important components of $PM_{2.5}$ and PM_{10} include polycyclic aromatic hydrocarbons (PAHs), a group of organic contaminants that form during combustion of hydrocarbons, such as coal, diesel, gasoline, wood, cigarettes and food items and food preparation (6). PAHs are ubiquitous environmental contaminants that can be due to occupational, dietary or airborne sources. The current study focuses on ambient PAHs found in the environment primarily as a result of automobile exhaust and industrial emissions.

Long-term exposure to ambient PAHs has been associated with increased risks of morbidity (7-13) and mortality (14, 15)(16, 17). . Perera *et al*. proposed that placental transfer of PAHs to the fetus have an impact on fetal development (18). Evidence from experimental studies demonstrate that benzo[a]pyrene (BaP) crosses the placenta (19) and has been classified by the U.S. Environmental Protection Agency (EPA) as a probable human carcinogen. Furthermore, animal studies have indicated PAHs may influence gestational length and intrauterine growth (20) and human studies have associated urinary and blood biomarkers of exposures to PAHs with birth weight (21) and gestational length (22).

PAH exposure is ubiquitous and detected in pregnant women (23, 24). Studies suggest that exposure to ambient PAH during pregnancy is related to adverse birth outcomes including low birth weight (25, 26), preterm birth (27, 28), intrauterine growth retardation (28, 29), and early pregnancy fetal death (30). However, a lack of adequate air monitoring data has limited our understanding of the effects of airborne PAHs on adverse birth outcomes. A recent study of traffic-related air toxics and preterm birth recommended future studies to focus on 1) PAHs and 2) accurate modeling of both local and regional spatial and temporal distributions, and incorporation of source information (27).

The current study extends previous work that found associations between $PM_{2.5}$ and PM_{10} and preterm birth, with stronger associations with earlier gestational ages (*i.e*., <27 weeks gestation) in the San Joaquin Valley (5). Here we evaluate associations between exposure to ambient PAHs during specific periods of pregnancy and preterm birth in Fresno, California during years 2001-2006. Fresno is a highly polluted city in California with a high prevalence of adverse health outcomes including premature mortality and asthma (31).

METHODS

Study population

The study population is a subset of the Study of Air pollution, Genetics and Early life events (SAGE). The entire study population has been described previously (5, 32). The population subset was selected because of its proximity to intensive monitoring of PAHs in the Fresno area during these years.

Outcome ascertainment

Analyses were limited to singleton births between 20 and 42 weeks gestation and birth weight between 500 and 5000 grams. Preterm birth was defined by gestational age at birth as determined from the last menstrual period on the birth certificate. Preterm birth is a complex phenomenon and a simple dichotomous definition has been argued to be too simplistic for etiologic studies owing to the heterogeneity that has been observed with this outcome (33). Four categories of preterm birth were created based on gestational ages: 20-27 weeks, 28-31 weeks, 32-33 weeks and 34-36 weeks. Term births (*i.e.*, 37-42 weeks) were considered the reference in all analyses.

Exposure assessment

Maternal residence at birth locations, as determined from birth certificates, were geocoded (point addresses) with Arc GIS software (Environmental Systems Research Institute, Redlands, CA, version 9). Addresses were corrected with ZP4 software (Semaphore Corporation, Aptos, CA) in ArcView and SAS (SAS Institute Inc., Cary, NC, version 9.2).

PAH exposure assignments were made if the geocoded residences were within 20 km (12.4 miles) of the First Street U.S. EPA air monitoring site in Fresno, California and were available for at least 75% of the exposure period during pregnancy. The study area included urban, suburban and rural areas. A combination of data including measurements made at the EPA air monitoring site of 4, 5 and 6 ring PAHs (PAH456) between 2000-2006, intensive air pollution sampling conducted at 83 locations in Fresno between February 2002 and February 2003, meteorological data, source data, and other spatial variables were used to form a spatio-temporal model to assign daily exposure to PAHs at the maternal residence throughout pregnancy of all births in the study area (34).

The model estimates the sum of PAHs including fluoranthene, benz[a]anthracene, chrysene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[ghi]perylene, indeno[1,2,3-cd]pyrene, and dibenz[a,h]anthracene. These PAHs represent semi-volatile PAHs of the original 16 priority PAHs that were identified by the U.S. EPA. This model explained 81% of the between-residence variability and 18% of the within-residence variability as measured by mixed-effects model variance components. Main sources of PAHs in Fresno are the freeways, major arterials, agricultural burns, residential fireplace and woodburning stove use, and heating (35). More detail on field collection, measurement results, and modeling can be found in Noth et al. (34).

Covariates

Variables from birth certificates included in analyses were: infant birth weight, maternal age (<20, 20-35, >35 years), maternal race/ethnicity (White, Hispanic, African-American, Asian, other), maternal education (no high school, some high school, some college, bachelors or other degree), parity (0, >1), prenatal care (initiated in first trimester or not), Medi-Cal (Medicaid) or other government program payment of birth expenses, infant sex, and birth year (2001-2006).

Socioeconomic status (SES), such as poverty and unemployment, has been associated with adverse birth outcomes (36). Furthermore, SES has been identified as an effect modifier in the relationship between air pollution and adverse birth outcomes (5, 37-40). Based on measures implemented in a previous study (40), we created an indicator variable for low SES that was defined as unemployment >10 percent, income from public assistance >15 percent, and families below poverty level >20 percent in the 2000 U.S. Census at the block group level (40, 41). Such an indicator may not pertain directly to any individual, but provides contextual information about study population neighborhoods. This research was approved by the University of California, Berkeley Office for Protection of Human Subjects, Stanford University Institutional Review Board, and the California State Committee for the Protection of Human Subjects.

Statistical Analyses

First, second, and third pregnancy trimesters were defined as gestational weeks 1-13, 14-26, and 27 to birth, respectively. The exposure period for pregnancy began 14 days after the first day of the last menstrual period. Additionally, we calculated metrics for the last 6 weeks of pregnancy (birth minus 42 days). We used logistic regression to examine the association between the highest quartile of PAH456 compared to the lower three and each of the four gestational definitions of preterm birth (20-27 weeks, 28-31 weeks, 32-33 weeks and 34-26 weeks) versus term (37-42 weeks). Exposure periods of the term births were truncated to match the same period as the comparison period-length of the preterm births.

The distributions of several covariates were also examined in relation to the PAHs and preterm birth distributions: maternal age, maternal race/ethnicity, maternal education, parity, prenatal care, Medi-Cal birth expenses payment, infant sex, neighborhood SES, season of conception, and birth year.

Exposures were categorized as “high” if they were above the 75%-ile of entire pregnancy averages. First, second, and third pregnancy trimesters were defined as gestational weeks 1-13, 14-26, and 27 to birth, respectively. We used logistic regression to examine associations between PAH456 during each trimester and the last 6 weeks of pregnancy and the four gestational definitions of prematurity (20-27 weeks, 28-31 weeks, 32-33 weeks and 34-36 weeks) versus term (37-42 weeks). Previous analyses of this cohort indicated the last 6 weeks of pregnancy may be a critical period for the association between particulate matter and early preterm birth (5).

We adjusted models for the following covariates: maternal age, race/ethnicity, education, prenatal care in the first trimester, and Medi-Cal payment of birth costs. We stratified by

neighborhood SES and season of conception to determine whether either factor modified an effect of PAH exposures on preterm birth. Analyses were restricted to births without reported maternal diabetes (types 1 and 2, and gestational) or hypertension (chronic, gestational and preeclampsia) owing to the known association between these morbidities and preterm birth.

All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, 2012).

RESULTS

The characteristics of the study population of 42,904 births are presented in Table 1 by gestational age category. Most study mothers were Hispanic, had Medi-Cal payment of birth costs, and had at least a high school education.

PAH exposures during pregnancy had a median of 3.6 ng/m^3 with an interquartile range of 1.6 ng/m^3 and a range of 12.4 ng/m^3. PAH exposures over the entire pregnancy were correlated with outdoor $PM_{2.5}$ (ρ=0.53) and PM_{10} (ρ=0.38) as well as traffic density within 300m of the home (ρ=0.30) (ρ is defined as the Pearson correlation coefficient). The distribution of PAH exposures by gestational age category is presented in Table 2.

Table 3 displays the relation between PAH exposures during different periods of pregnancy and the four gestational week definitions of preterm birth. Associations were observed between PAH exposures during the last 6 weeks of pregnancy and birth at 20-27 weeks (OR=2.74; 95% CI: 2.24-3.34) comparing the highest quartile to the lower three quartiles. When examined for an exposure-response, the association increased across each quartile of PAH exposures. Inverse associations were also observed for exposure to PAHs during the entire pregnancy and the first trimester and birth at 28-31 weeks and 20-27 weeks.

Stratification by neighborhood SES showed little differences between groups. For births conceived during summer (June-August), associations were statistically significant for each category of preterm birth and exposure to PAHs during the last 6 weeks with odds ratios ranging from 2.5 (95% CI: 2.1, 2.9) for birth at 34-36 weeks to 10.2 (95% CI: 7.8, 13.4) for birth 20-27 weeks (Table 4). Inverse associations were observed for those conceived in the spring (March-May).

DISCUSSION

Our study shows an association between elevated levels of PAH456 during the last 6 weeks of pregnancy and early preterm birth (i.e., <27 weeks gestation) in Fresno, California with risk increasing with increasing quartiles of exposure. However, inverse associations with early preterm birth were also observed for the first trimester and entire pregnancy metrics of PAH exposures. The biologic explanation for the latter is unknown. It could be hypothesized that highly exposed pregnancies were spontaneously aborted during the first trimester creating a bias among the survived births; however, we do not have the data in this study to address such a question.

Ambient PAH levels vary by season in Fresno, with higher levels in the winter. Preterm birth also varies by season, especially in Fresno during these years, but it is unknown whether such preterm birth variation is because of PAHs or an unknown and highly correlated factor. It is unclear if or when a critical period may exist for risk of preterm birth; though this study and its larger cohort have found the last 6 weeks (which also corresponds to the second trimester for early preterm birth) to have the strongest associations.

A few previous studies of PAH exposures and preterm birth have been conducted. A recent study found an association between PAH exposure (as predicted by an EPA Chemical Mass Balance model) and preterm birth in another geographic are of California, i.e., Los Angeles (27). However, no clear pattern indicating specific gestational periods of greater susceptibility were observed in this population.

A study in New York City found associations between PAH exposure during pregnancy and preterm birth among African Americans; however, the associations was not seen among Dominicans. A 1-ln-unit increase in prenatal PAH exposure was associated with a 5-fold greater risk of preterm birth for African Americans (28).

Our study is subject to certain limitations. Estimation of personal exposure to air pollutants using ambient monitoring data suffers from potential exposure misclassification due to intra-urban variability in outdoor concentrations of pollutants (42). This misclassification would likely bias our estimates toward the null since the quartiles held a generally consistent exposure response relationship. Although we have precise information of the maternal residence at birth, we do not have data on residential mobility or workplace location. We lack data on other sources of PAHs including cigarette smoke (active and passive), dietary ingestion and indoor or occupational sources such as cooking. There are additional potential confounders for which we do not have data, including maternal pre-pregnancy BMI and nutrition.

The strengths of our study include comprehensive spatio-temporal modeling of PAHs over 6 years in a highly exposed region of the country. The model was able to show both temporal and spatial variation by using a mixed-effects regression model based on measurement data combined with source, land use, and neighborhood characteristics. The model generated the daily spatial distribution of outdoor residential PAH456 concentrations in Fresno, as well as individual exposure estimates for each participant. Daily estimates were combined to provide pregnancy-specific exposure estimates. Previous work describing the spatial distribution of PAHs has been limited primarily to source-to-receptor studies (43, 44), small neighborhoodsized areas (45) or to large-scale regional or national annual distributions (46-50). While each of these approaches is useful for certain situations, such as for policy recommendations or long-term exposure studies, they cannot address the impact of short-term exposure on acute health outcomes as our daily model can.

In conclusion, ambient PAH exposure in the last 6 weeks of pregnancy may be associated with increased risk of early preterm birth. However, given the mixed results, more studies are needed to determine the relationship between PAHs and early preterm birth.

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Abbreviations

CI	confidence interval
PAHs	polycyclic aromatic hydrocarbons
PM	particulate matter
SAGE	study of air pollution, genetics and the environment
SES	socioeconomic status

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Highlights

- Spatio-temporal models estimated exposure to ambient PAH during pregnancy.
- PAH exposure in the end of pregnancy was associated with early preterm birth.
- Seasonal differences in PAH and preterm birth are apparent in Fresno, California.

Table 1

Characteristics of the study population, total and by preterm birth (%)

Characteristic	Gestational age in weeks					Total n=42,904
	37-42 n=37,158	34-36 n=3940	32-33 n=757	28-31 n=605	20-27 n=444	
Maternal age (years)						
<20	14.0	15.7	14.7	18.4	17.6	14.3
20-24	30.3	30.4	32.4	32.7	34.9	30.4
25-29	27.0	25.7	23.8	22.8	23.0	26.7
30-34	18.5	16.9	16.8	14.1	15.1	18.2
≥35	10.2	11.3	12.4	12.1	9.5	10.4
Maternal race/ethnicity						
White	26.8	22.6	18.9	15.2	14.6	26.0
Hispanic	53.8	54.9	56.7	55.7	59.5	54.0
Black	7.0	9.2	11.6	13.4	8.3	7.4
Asian	10.7	11.6	10.8	13.6	14.2	10.8
Other	1.8	1.7	2.0	2.2	3.4	1.8
Maternal education						
<High school	10.2	9.8	12.4	12.2	13.1	10.3
High school	51.2	57.4	59.1	65.0	63.3	52.2
Some college	21.9	20.2	18.8	16.5	16.2	21.6
College or other degree	15.4	11.0	8.2	4.5	5.4	14.6
Missing	1.3	1.6	1.6	1.8	2.0	1.3
Initiation of prenatal care						
Before 1st trimester	88.2	83.9	80.3	77.9	75.9	87.4
After 1st trimester	11.2	14.8	17.8	18.8	18.9	11.9
Missing	0.6	1.3	1.9	3.3	5.2	0.7
Parity						
0	35.5	31.0	30.5	26.9	29.5	34.9
≥1	64.5	69.0	69.5	73.1	70.5	65.2
Infant sex						
Male	51.1	54.6	52.1	54.7	58.3	51.6
Female	48.9	45.4	48.0	45.3	41.7	48.4
Low neighborhood SES	30.4	34.8	38.2	41.8	42.1	31.2
Medi-Cal payment	58.6	65.4	68.3	74.4	77.7	59.8
Cesarean section	26.9	28.8	34.2	33.2	36.7	27.4
Season of conception						
Winter (December-February)	25.5	23.0	19.7	15.9	11.5	24.9
Spring (March-May)	24.8	26.0	26.6	19.2	14.4	24.8
Summer (June-August)	23.9	24.4	30.4	45.5	60.8	24.8

Characteristic	Gestational age in weeks					Total n=42,904
	37-42 n=37,158	34-36 n=3940	32-33 n=757	28-31 n=605	20-27 n=444	
Fall (September-November)	25.7	26.7	23.4	19.5	13.3	25.6
Year of birth						
2001	11.4	9.7	7.0	8.4	5.4	11.1
2002	14.7	14.4	12.4	9.8	5.9	14.5
2003	15.8	15.5	13.1	12.4	9.5	15.6
2004	17.4	17.1	15.3	9.4	10.1	17.2
2005	19.5	20.9	21.5	28.3	38.5	20.0
2006	21.1	22.4	30.7	31.7	30.6	21.7

Table 2

Median (interquartile range) of PAHs (ng/m^3) for each exposure period by gestational age categories.

Exposure period	Gestational age in weeks					Total
	37-42	34-36	32-33	28-31	20-27	
Entire pregnancy	3.57 (1.59)	3.49 (1.66)	3.43 (1.66)	3.41 (1.48)	3.22 (1.30)	3.55 (1.59)
1st trimester	3.18 (1.70)	3.14 (1.63)	3.07 (1.73)	2.97 (1.41)	2.74 (1.15)	3.17 (1.69)
2nd trimester	3.11 (1.58)	3.12 (1.60)	3.22 (1.60)	3.44 (1.52)	3.50 (1.44)	3.12 (1.58)
3rd trimester	3.09 (1.50)	3.06 (1.60)	3.06 (1.56)	3.27 (1.53)	3.06 (1.74)	3.09 (1.51)
Last 6 weeks	3.01 (1.69)	3.02 (1.66)	3.06 (1.66)	3.28 (1.46)	4.11 (2.12)	3.03 (1.69)

Table 3

Adjusted[a] odds of birth at each gestational age for exposure to the highest quartile versus lower three quartiles of PAHs during each exposure period and 95% confidence intervals compared to term (gestational age at 37-42 weeks).

PAH exposure period	Gestational age in weeks											
	34-36			32-33			28-31			20-27		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Entire Pregnancy	0.99	0.92	1.07	0.93	0.79	1.11	**0.76**	0.62	0.93	**0.51**	0.39	0.67
1st trimester	0.92	0.84	1.00	0.87	0.72	1.05	**0.56**	0.44	0.71	**0.42**	0.31	0.58
2nd trimester	0.98	0.89	1.07	1.03	0.85	1.24	1.02	0.83	1.25	1.10	0.81	1.49
3rd trimester	1.00	0.92	1.09	0.99	0.81	1.19	1.00	0.81	1.23	NC	--	--
Last 6 weeks	0.96	0.88	1.05	0.97	0.80	1.16	0.86	0.70	1.07	**2.74**	2.24	3.34

Gestation at 20-27 weeks PAHs during last 6 weeks	Odds Ratio	95% CI	
2nd quartile	**1.49**	1.08	2.06
3nd quartile	**2.63**	1.93	3.59
4th quartile	**3.94**	3.03	5.12

Abbreviations: PAHs, polycyclic aromatic hydrocarbons; OR, odds ratio; CI, confidence interval

[a]Models adjusted for maternal age, education, race/ethnicity, prenatal care in the first trimester and payment of birth expenses

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Table 4

Season of conception-stratified, adjusted[a] odds of birth at each gestational age for exposure to the highest quartile versus lower three quartiles of PAHs during each exposure period and 95% confidence intervals compared to term (gestational age at 37-42 weeks).

Season of conception	PAH exposure period	Gestational age											
		34-36 weeks			32-33 weeks			28-31 weeks			20-27 weeks		
		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Winter	Entire Pregnancy	0.97	0.80	1.19	1.07	0.67	1.70	**2.43**	1.52	3.87	1.05	0.47	2.37
	1st trimester	**0.80**	0.68	0.95	0.94	0.64	1.37	1.07	0.65	1.76	0.63	0.30	1.29
	2nd trimester	1.00	0.69	1.43	0.36	0.09	1.47	1.81	0.78	4.19	0.95	0.13	7.09
	3rd trimester	0.82	0.57	1.18	1.80	0.96	3.38	1.31	0.53	3.26	NC	--	--
	Last 6 weeks	**0.57**	0.39	0.83	1.53	0.84	2.80	1.21	0.52	2.79	0.78	0.19	3.26
Spring	Entire Pregnancy	**0.66**	0.54	0.80	**0.41**	0.25	0.68	**0.20**	0.08	0.50	**0.15**	0.04	0.63
	1st trimester	1.20	0.87	1.65	1.22	0.64	2.34	0.43	0.11	1.75	0.85	0.20	3.52
	2nd trimester	0.87	0.62	1.22	1.41	0.79	2.51	0.18	0.03	1.32	0.49	0.07	3.56
	3rd trimester	**0.76**	0.66	0.87	**0.47**	0.34	0.64	0.74	0.50	1.10	NC	--	--
	Last 6 weeks	**0.50**	0.44	0.58	**0.27**	0.20	0.37	**0.27**	0.18	0.41	**0.04**	0.01	0.11
Summer	Entire Pregnancy	1.15	0.99	1.33	0.91	0.68	1.21	**0.42**	0.31	0.59	**0.18**	0.11	0.28
	1st trimester	1.06	0.76	1.50	0.91	0.48	1.74	**0.22**	0.07	0.70	**0.22**	0.07	0.69
	2nd trimester	0.93	0.80	1.08	0.72	0.54	0.96	**0.40**	0.30	0.53	**0.47**	0.32	0.67
	3rd trimester	1.25	1.07	1.45	1.15	0.85	1.57	0.78	0.58	1.03	NC	--	--
	Last 6 weeks	2.45	2.09	2.88	**2.95**	2.17	4.02	**2.17**	1.62	2.9	**10.2**	7.8	13.4
Fall	Entire Pregnancy	1.08	0.94	1.23	1.22	0.90	1.67	1.14	0.78	1.69	**2.73**	1.57	4.74
	1st trimester	0.97	0.83	1.12	1.23	0.87	1.73	0.88	0.58	1.33	1.75	0.95	3.23
	2nd trimester	0.93	0.79	1.08	0.86	0.59	1.25	1.02	0.67	1.55	0.65	0.29	1.44
	3rd trimester	0.86	0.60	1.24	0.77	0.31	1.89	0.24	0.03	1.73	NC	--	--
	Last 6 weeks	0.77	0.58	1.04	0.70	0.34	1.42	**0.13**	0.02	0.95	**3.80**	1.93	7.5

Abbreviations: PAHs, polycyclic aromatic hydrocarbons; OR, odds ratio; CI, confidence interval

[a]Models adjusted for maternal age, education, race/ethnicity, prenatal care in the first trimester and payment of birth expenses