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Newborn infant urinary cotinine and birth outcomes in the Jerusalem Environment Mother and Child Cohort Study

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ABSTRACT

Background: Environmental tobacco smoke (ETS) exposure during pregnancy can cause preterm delivery and childhood cancer. The aim of this study was to measure ETS exposure in pregnant women and in newborn infants in Israel using urinary cotinine measurements, to assess predictors of ETS exposure in these vulnerable groups, and to assess associations with birth effects (birth weight, birth length, head circumference) in newborn infants.
Methods: We analyzed urinary cotinine and creatinine in 265 non-smoking pregnant women and 97 newborns, and analyzed associations with self-reported exposure to ETS, paternal smoking, sociodemographic variables and with birth outcomes (birth weight, birth length, head circumference).
Results: 37.7% of pregnant women and 29.0% of infants had urinary cotinine concentrations above the level of quantification (LOQ) of 1 μg/L, whereas 63.8% and 50.5%, respectively, had urinary cotinine concentrations above the level of detection (LOD) of 0.5 μg/L. Median unadjusted and creatinine adjusted urinary concentrations of cotinine in pregnant women were 0.7 μg/L, and 0.9 μg/g creatinine, respectively, and in newborn infants were 0.5 μg/L, and 1.3 μg/g creatinine, respectively. We did not find an association between maternal and infant urinary cotinine level. Maternal (but not infant) urinary cotinine was significantly associated with paternal smoking ($p < 0.05$). Infant (but not maternal) cotinine above the LOQ was negatively associated with birth weight ($p < 0.05$).
Conclusions: In this high socioeconomic cohort, almost a third of newborn infants born to non-smoking mothers had quantifiable levels of urinary cotinine. This is the first study showing that newborns with quantifiable urinary cotinine levels have lower birth weight.

1. Introduction

The developing fetus is uniquely vulnerable to toxicants, including tobacco constituents. The adverse effects of nicotine on the developing fetus – including increased spontaneous abortions in the first trimester, increased premature delivery rates, and decreased birth weights in the third trimester - are well known. Nicotine readily gains access to the fetal compartment via the placenta, with fetal concentrations generally 15% higher than maternal levels (Lambers and Clark, 1996). Smoking during pregnancy leads to decreased transfer of nutrients and oxygen to the fetus and is associated with sudden infant death syndrome (Haglund and Cnattingius, 1990; Difranza and Lew, 1995; Anderson and Cook, 1997; Castles et al., 1999) visual problems in adult life (Fernandes et al., 2015) cognitive and neurodevelopmental delay (Weitzman et al., 2002) and Attention-Deficit/Hyperactivity Disorder (ADHD) (Huang et al., 2018a).

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Exposure to environmental tobacco smoke (ETS) is also associated with a wide range of adverse development effects in the fetus. There is evidence that exposure to ETS causes sudden infant death syndrome and a small reduction in birth weight and suggestive evidence that ETS causes preterm delivery and childhood cancer (Centers for Disease Control and Prevention, 2006). There is evidence that ETS exposure during pregnancy can have a negative impact on child psychomotor and mental development within the first two years of life (Polanska et al., 2017; Lee et al., 2019).

Fetal exposure to ETS can be quantified by measuring maternal cotinine in blood and urine, and nicotine in hair and by measuring cotinine in umbilical cord blood and in urine, blood, and meconium in newborns (Spector et al., 2014). Abdullah et al. (2017) reported that cord blood cotinine levels of newborns whose mothers reported they were exposed to ETS were significantly higher than those of newborns whose mothers reported they were not exposed to ETS (Abdullah et al., 2017). Tsinisizeli et al. (2015) found that cotinine concentrations in meconium were significantly higher in newborns born to smoking mothers and non-smoking mothers that were exposed to ETS (Tsinisizeli et al., 2015). Mansi et al. found that urinary cotinine in newborns is correlated with the number of maternal daily smoked cigarettes (Mansi et al., 2007).

ETS exposure in Israel is widespread in infants, children and adults. Over 60% of both adult non-smokers and children in Israel are exposed to ETS, based on urinary cotinine measurements in 2015–2016 (Berman et al., 2018a; Berman et al., 2018b). In addition, 25% of Jewish infants and 52% of Arab infants are exposed to ETS at two months of age (based on maternal self-report) (Israel Ministry of Health, 2014). Data on urinary cotinine in pregnant women and their newborns have not been reported previously. The aims of this study were: (1) to measure ETS exposure in pregnant women and newborns using urinary cotinine measurements, (2) to assess predictors of ETS exposure in this population, and (3) to explore associations between maternal and infant cotinine and birth outcomes.

2. Materials and methods

2.1. Study population

The '*Mother, Child and the Environment*' study is an ongoing population-based birth cohort established in September 2012. Pregnant women (mean gestational age at recruitment: 13.7 ± 2.2 weeks) from Jerusalem and its surroundings were recruited at the ultrasonography unit of Hadassah Medical Organization or in one of the clinics of Clalit Health Maintenance Organization (HMO) in Jerusalem. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and has been approved by the Ethics committees of Hadassah Medical Centers and Clalit HMO. The study included healthy women with spontaneous, singleton pregnancies of less than 18 weeks at recruitment, who intended to give birth in one of the two campuses of the Hadassah Medical centers. All participants signed an informed consent form, were interviewed and provided spot urine samples. Questionnaires included demographic, occupational and health data, as well as information regarding health perception, use of medication, use of self-care products, diet including fruit consumption, and obstetric history. Women were specifically asked about their smoking habits, their husband's smoking habits, and their exposure to ETS. During the first 72 h following birth, neonatal urine samples of 5 cc were collected from infants using urine collection bags and the study neonatologist performed anthropometric measurements of the newborn (head circumference and birth length). In addition, birth outcomes were collected from the institutional electronic log files including neonatal birth weight.

2.2. Analysis of urine samples

Urinary cotinine and creatinine were measured in 275 pregnant women and 97 newborns. Maternal samples were collected at the time of maternal recruitment (before week 18 of pregnancy) at Hadassah Medical Center or at Clalit clinics in Jerusalem between September 2012 and March 2016. Neonatal urine samples were respectively collected between March 2013 and December 2016, at Hadassah Hospital, within 72 h after birth using urine collection bags. All urine samples were collected in polypropylene tubes and stored at −80 °C until analysis. Samples were shipped to the University of Erlangen–Nuremberg in Germany on dry ice (−80 °C), and were analyzed for cotinine and creatinine. Researchers at the University of Erlangen–Nuremberg had no access to details on participant's identification.

Cotinine in urine was determined using gas chromatography mass spectrometry (Müller et al., 2003). In brief, cotinine was extracted from the urine using dichloromethane and quantified after gas chromatographic separation by mass spectrometry in single ion monitoring mode. Deuterated cotinine was used as an internal standard. Limit of detection (LOD) was 0.5 µg/L and limit of quantification (LOQ) was 1 µg/L. Creatinine in urine was determined by photometric detection according to the Jaffé method (Larsen, 1972). Quality control was performed by analyzing aliquots of control material in each series and accuracy was validated by the successful participation in G-EQUAS for both parameters (Göen et al., 2012).

Urinary analyte concentrations were provided in units of µg/L. In order to correct for variable dilutions among spot samples, these concentrations were divided by urinary creatinine concentrations (g creatinine/L urine) to generate creatinine-adjusted analyte concentrations.

2.3. Statistical analysis

Since most urinary concentrations were below the LOQ we conducted analyses with cotinine as a dichotomous variable - below or above the LOQ; and as below or above the LOD. We calculated percent of participants with urinary cotinine above the LOD and LOQ.

In addition, we analyzed urinary cotinine as a continuous variable. We imputed concentrations below the LOD using maximum likelihood estimation based on a log-normal distribution truncated at the LOD (Engel et al., 2016). We calculated urinary concentrations of maternal and neonatal cotinine (mean, median, percentiles), both unadjusted and adjusted for creatinine.

We calculated the association between maternal and infant urinary cotinine level (below and above LOQ) using the chi-square test, and Pearson correlation for continuous data. Univariate analysis was conducted to explore associations between baseline maternal characteristics and maternal and infant urinary cotinine (as dichotomous variable) using the chi square test for significance. We also conducted univariate analyses using continuous cotinine level (unadjusted for creatinine) and demographic characteristics as categorical variables, using one way ANOVA. The association between maternal self-reported exposure to ETS and cotinine level in urine (as continuous variable, not adjusted for creatinine) was analyzed using one way ANOVA. Associations between birth outcomes and maternal and infant urinary cotinine levels were calculated using the *t*-test. Multivariable linear regression models were performed to analyze the associations between maternal and infant urinary cotinine level (as dichotomous variables, above and below LOD and LOQ, and as continuous variable) with birth outcomes (birth weight, birth length, head circumference). All models were adjusted for maternal weight at the beginning of pregnancy and infant's sex.

In addition we used linear regression models to analyze the associations between maternal cotinine and infant cotinine (using continuous data).The level of significance was 0.05 in all analyses.

Table 1
Characteristics of pregnant women (n = 265) and infants (n = 93).

	Mean (± std)		Median
Maternal age (years)	32.2 ± 5.4		32.0
Maternal BMI (kg/m^2)	23.7 ± 4.3		22.7
Gestational age at recruitment (weeks)	13.5 ± 2.2		12.9
Birth weight (g)	Boys (n = 58)	3349.2 ± 522.4	3381
	Girls (n = 35)	3300.8 ± 504.2	3268
Birth Length (cm)	Boys (n = 58)	51.0 ± 2.2	51.2
	Girls (n = 35)	51.0 ± 2.4	51.3
Head circumference at birth (cm)	Boys (n = 58)	34.7 ± 1.5	35.0
	Girls (n = 35)	34.1 ± 1.4	34.3

3. Results

Out of 275 pregnant women, we excluded seven women who reported that they were smokers. In addition, we excluded three women who reported that they were non-smokers but with urinary cotinine above 150 μg/g creatinine (Heinrich et al., 2005), resulting in 265 non-smoking pregnant women. Out of 97 neonates, we excluded 4 due to maternal smoking during pregnancy (reported smoking or urinary concentrations above 150 μg/g creatinine).

Mean maternal age was 32.2 years (std 5.4). For 20% of the women, this was the first pregnancy; 73.5% of women were highly educated (above 13 years, see Tables 1 and 3). Mean birth weight, length and head circumference in infants is shown in Table 1.

37.7% of the women had urinary cotinine above the LOQ (1 μg/L) and 63.8% had urinary levels above the LOD (0.5 μg/L). 29.0% of infants of non-smoking mothers had urinary cotinine above the LOQ and 50.5% had urinary cotinine above the LOD. Median unadjusted and creatinine adjusted urinary concentrations of cotinine in pregnant women were 0.7 μg/L, and 0.9 μg/g creatinine, respectively, and in newborn infants were 0.5 μg/L, and 1.3 μg/g creatinine, respectively (Table 2). Maternal and infant's urinary cotinine concentrations (μg/L) were not significantly associated ($r = 0.16$, $p > 0.1$).

Maternal urinary cotinine (above and below the LOQ) was not associated with maternal education, paternal education, or self-reported exposure to ETS. Maternal urinary cotinine (above or below the LOQ) was significantly associated with paternal smoking ($p < 0.05$) (Table 3). There was a trend for higher cotinine in pregnant women whose husband was a current smoker (1.1 μg/L) compared to those whose husband smoked in the past (0.82 μg/L) and those whose husband never smoked (0.6 μg/L, $p = 0.12$). In a univariate analysis using dichotomous data, no association was found between maternal cotinine level and infant birth weight, length, or head circumference.

Infant urinary cotinine levels were not associated with maternal education, paternal education, and paternal smoking, either when studied as a dichotomous (below or above the LOQ, Table 4), or as a continuous variable (not shown). In the analysis using continuous data (unadjusted for creatinine), infants born to women who reported that they were moderately exposed to ETS had higher mean urinary cotinine concentrations (11.8 ± 27.7 μg/L) than infants born to women who reported that they were barely (1.04 ± 1.6 μg/L) or not (1.04 ± 1.2 μg/L) exposed to ETS, ($p < 0.05$).

In linear regression models, adjusting for maternal weight at pregnancy and infant's sex, maternal cotinine levels were not significantly associated with infant birth weight, length, or head circumference (not shown). In contrast, infant cotinine in urine (as dichotomous variable higher or lower than LOD) was negatively associated with birth weight ($p < 0.05$) and head circumference ($p < 0.05$). Infant cotinine in urine (as dichotomous variable higher or lower than LOQ) was negatively associated with birth weight ($p < 0.05$) (Table 5). In the multivariable model, urinary cotinine as a continuous variable was not significantly associated with birth weight,

Table 3
Baseline characteristics in pregnant women with maternal urinary cotinine concentrations below or above the level of quantification (n = 265).

	N = 265	Urinary Cotinine Below or Above LOQ of 1 μg/L		P-value
		Below	Above	
		N = 165	N = 100	
Maternal education (years)				
0–12	27%	27%	26%	> 0.1
13–16	32%	31%	35%	
17+	41%	43%	39%	
Paternal education (years)				
0–12	34%	32%	39%	> 0.1
13–16	31%	35%	26%	
17+	34%	34%	36%	
Maternal self-report to ETS				
No	46%	50%	39%	> 0.1
Barely	47%	45%	52%	
Moderate	5%	4%	6%	
Very exposed	1.5%	0.6%	3%	
Paternal smoking				
No	59%	66%	48%	< 0.05
In past	23%	20.4%	27%	
Currently	18%	13.6%	25%	
Birth outcomes[a] **(mean ± std)**				
Gestational age (days)	274 ± 11	274 ± 11	273 ± 11	> 0.1
Birth weight (g)	3274 ± 488	3274 ± 494	3276 ± 482	> 0.1
Birth length (cm)	51.0 ± 2.4	51.1 ± 2.2	50.8 ± 2.6	> 0.1
Head circumference at birth (cm)	34.3 ± 1.4	34.3 ± 1.3	34.4 ± 1.4	> 0.05

Footnote: statistical test by chi square.
[a] no significant differences after stratification by gender.

Table 2
Urinary cotinine concentrations (unadjusted and adjusted for creatinine) in maternal (n = 265) and infant's (n = 93) urine.

	Above LOD (%)	Above LOQ (%)	Median	25th percentile	75th percentile	95th percentile	Max
Maternal exposure							
Cotinine (μg/L)	63.8	37.7	0.7	0.3	1.5	3.1	54.0
Cotinine (μg/g creatinine)			0.9	0.5	1.9	7.8	146.4
Infant exposure							
Cotinine (μg/L)	50.5	29.0	0.5	0.2	1.2	4.2	68.2
Cotinine (μg/g creatinine)			1.3	0.4	3.4	21.9	220.3

Table 4
Baseline characteristics in infants with urinary cotinine concentrations below or above the level of quantification (n = 93).

	Total (%)	Urinary Cotinine Below or Above LOQ of 1 μg/L		P-value
		Below	Above	
	N = 93	N = 66	N = 27	
Maternal education (years)				
0–12	28%	27%	31%	> 0.1
13–16	29%	25.4%	39%	
17+	43%	48%	31%	
Paternal education (years)				
0–12	37%	36%	39%	> 0.1
13–16	29%	30%	27%	
17+	34%	34%	35%	
Maternal self-report to ETS				
No	49%	46%	56%	> 0.1
Barely	44%	46%	37%	
Moderate	7%	6%	7%	
Very exposed	1%	2%	0%	
Paternal smoking				
No	63%	65%	59%	> 0.1
in past	21%	19%	26%	
Currently	16%	17%	15%	
Birth outcomes[a] (mean ± std)				
Gestational age (days)	273.5 ± 10.3	273.3 ± 10.1	274 ± 10.1	> 0.1
Birth weight (g)	3331 ± 513	3392 ± 505	3180 ± 510	> 0.05
Birth length (cm)	51 ± 2.3	51 ± 2.2	51 ± 2.5	> 0.1
head circumference at birth (cm)	34.5 ± 1.5	34.6 ± 1.4	34.2 ± 1.7	> 0.1

Footnote: statistical test by chi square.
[a] no significant differences after stratification by gender.

Table 5
Results of linear regression models between infant cotinine in urine and birth effects*.

	Cotinine as Continuous Variable		Cotinine as Dichotomous Variable (Above or Below LOQ)		Cotinine as Dichotomous Variable (Above or Below LOD)	
	Beta estimate	P-value	Beta estimate	P-value	Beta estimate	P-value
Birth weight	0.01	> 0.1	−0.66	< 0.05	−0.85	< 0.05
Birth length	0.02	> 0.1	−0.14	> 0.1	−0.41	> 0.1
Head circumference	0.01	> 0.1	−0.24	> 0.1	−0.47	< 0.05

*Models adjusted for maternal weight at pregnancy and infant's sex.

length, or head circumference (Table 5).

4. Discussion

In our cohort of highly educated pregnant women in the Jerusalem area, over 35% of pregnant women and over 25% of infants were exposed to ETS; and paternal smoking was associated with maternal cotinine but not with infant cotinine. In addition, newborns with quantifiable urinary cotinine levels had lower birth weight.

The percent of women and infants exposed to ETS (urinary cotinine above the LOQ) was low compared to our previous studies in adults and children, in which over 60% had urinary cotinine levels above the LOQ (Berman et al., 2018a; Berman et al., 2018b). There are several explanations for these results. First, as opposed to our previous study in non-smoking adults from varied socioeconomic backgrounds, ethnicities and geographical areas, the current study included mostly highly educated women. Active smoking rate in this cohort was low (2.5%) compared to the general population of pregnant women in Israel (estimated at 3.7% among pregnant women receiving health coverage from Meuhedet Health Services, personal communication). Next, it is likely that pregnant women avoid smokers therefore reducing their potential exposure to ETS. (Blake et al., 2009).

In pregnant women in our cohort, median cotinine concentrations (0.7 μg/L) were low compared to a cohort of non – smoking pregnant women in Korea (1.9 μg/L) (Lee et al., 2019). In newborn infants, mean urinary cotinine levels (1.7 μg/L) were similar to those reported in 25 newborn infants born to non-smoking women in Greece (1.9 μg/L) (median not reported) (Mansi et al., 2007).

Our finding that maternal urinary cotinine levels are associated with paternal smoking is in agreement with previous studies (Taylor et al., 2014) and emphasizes the impact of paternal smoking on maternal exposure to ETS. Our finding that maternal but not infant urinary cotinine was associated with paternal smoking is likely related to the fact that questionnaire data (on paternal smoking) was collected at the time of collection of maternal urine in early pregnancy. It is possible that some fathers stopped smoking or stopped smoking near their pregnant wives during pregnancy (Bottorff et al., 2009). Urinary cotinine concentration in infants was associated with self reported maternal exposure to ETS in early pregnancy. Further study, using questionnaire data collected near the time of urine sample collection, is needed.

The lack of association between maternal self-reported ETS and maternal urinary cotinine is consistent with our findings in the general adult population of non-smokers in Israel (Berman et al., 2018a). In that study, urinary cotinine concentrations and percent of participants with urinary cotinine above the LOQ, were not significantly higher in individuals reporting very high exposure to ETS. One possible explanation is that individuals may be unaware of actual exposure (Gee et al., 2013; Greenberg et al., 2013). Because 85% of smoke is invisible and smell is an unreliable indicator of exposure, many people may mistakenly believe that they are non-exposed, even though they actually are. Previous findings have found low validity of self-reported exposure to ETS during pregnancy (O'connor et al., 1995; George et al., 2006).

We found that infants with detectable urinary cotinine had lower birth weight and head circumference.These findings are consistent with previous reports on a negative association between birth weight and ETS exposure based on maternal self – reported exposure (Huang et al., 2018b; Owili et al., 2018), hair nicotine concentrations (Lee et al., 2015), maternal cotinine in saliva and serum (Salama et al., 2013), cord blood concentrations (Huang et al., 2017), and maternal urinary cotinine concentrations (Kalayasiri et al., 2018). On the other hand, Hedengran et al. (2018) reported that infants born to passive smokers, based on umbilical serum cotinine levels, did not have reduced birthweights.

The fact that birth weight and head circumference were associated with infant but not maternal cotinine is likely related to the fact that in our study, maternal cotinine reflects early pregnancy exposure whereas infant cotinine concentrations reflect late pregnancy exposure. Previous studies have shown that the strongest association between smoking and fetal growth restriction occurs in the third trimester (Blatt et al., 2015).

This study had several limitations. First, maternal urinary cotinine was measured using a single spot urine sample during pregnancy. Questionnaire data on paternal smoking and exposure to ETS was collected in early pregnancy and not at the time of urine sample collection from infants. Maternal urine samples were collected in early pregnancy, and not during the most relevant window of exposure for adverse effects of smoking on birth outcomes, since this study focused on additional contaminants with different windows of exposure. The study cannot be generalized to the entire Israeli population of pregnant women and infants. Since neonatal creatinine reflects maternal creatinine concentration at the time of delivery and not the neonate's kidney function (Benowitz et al., 2018), we present results of adjusted cotinine in infants, but did not adjust for creatinine in the model when looking at

birth effects. On the other hand, one of the strengths of the study is biological marker measurements in both infants and pregnant women and use of same analytical methods as studies in adults and children in Israel, making comparisons valid.

5. Conclusions

The results of our study revealed that in a cohort of highly educated non-smoking pregnant women in Jerusalem and its surrounding area, over 35% of pregnant women and 29% newborns are exposed to ETS. Results of our study highlight the potential impact of paternal smoking on maternal exposure to ETS and highlight the need for reducing ETS exposure in both pregnant women and infants. Moreover, the results indicate that perinatal ETS exposure may reduce birth weight and head circumference of the newborns. We recommend a nationally representative study on ETS in pregnant women and infants in Israel's diverse ethnic, socioeconomic, and geographic population. Furthermore, the lack of association between concentrations of maternal and infant urinary cotinine may indicate that measuring maternal exposure to ETS at one time point may be insufficient to represent exposure over the whole pregnancy. This should be considered in further studies.

Conflicts of interest

None declared.

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