J. Perinat. Med. 38 (2010) 689–692 • Copyright © by Walter de Gruyter • Berlin • New York. DOI 10.1515/JPM.2010.100

Original articles – Newborn

# Prenatal tobacco exposure and cortisol levels in infants of teen mothers

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## Abstract

**Aims:** Prenatal tobacco exposure (PTE) is an important public health concern for the offspring of teen mothers. We examined whether PTE is associated with baseline cortisol levels in four-month-old infants of teenage mothers.
**Methods:** We assessed salivary cortisol levels of 212 infants. PTE was measured by using self-reports of cigarette smoking during pregnancy. We used a propensity scores matching analysis to compare infants with PTE and those without.
**Results:** Of 212 mothers, 151 smoked during pregnancy. However, there was no association between PTE and infant cortisol levels.
**Conclusions:** We could not support a relation between PTE and cortisol levels in a sample of four-month-old infants of teenage mothers.

**Keywords:** Cortisol levels; infants; prenatal tobacco exposure (PTE); teen mothers.

## Introduction

Almost 17% of Canadian women who had a baby in the past five years smoked during pregnancy [20]. Although smoking has decreased slightly in Canada in the past five years, it remains significantly above the national level in the province of Quebec, where this study took place. This is especially true in youths from low socio-economic status [20]. Prenatal tobacco exposure (PTE) may alter the infant's hypothalamic-pituitary-adrenal (HPA) axis [14, 17]. In this paper, we examined cortisol levels in infants of teen mothers with PTE.

Adolescent smoking during pregnancy is of concern for several reasons. First, independent of tobacco, the body composition (fat and mass) in pregnancy is different between adolescent and adult women [21]. PTE during teen pregnancy could be associated with significantly lower birth weights in newborns, when compared to newborns of adult women with PTE [21]. Nevertheless, good nutrition status can increase birth size to normal ranges [21]. In contrast, smoking during teen pregnancies can be a risk factor for fetal growth restriction, low (<2.5 kg) birth weight and for preterm birth [8]. This risk might be even more pronounced when smoking is not accompanied by adequate nutrition. Second, adolescents use substances concomitantly [22, 27]. Third, once pregnant, many teens continue to display risky behaviors. Luckily, smoking is readily amenable to intervention [8].

Regardless of maternal age, PTE may have short- and long-term detrimental effects [7]. Some researchers [18] even regard it as being a form of *fetal neglect and abuse*. In the short run, PTE has been associated with several pregnancy complications, including placental problems [23] (although surprisingly, some studies showed an apparent ''protective'' effect of smoking on hypertension/eclampsia [26]). PTE is associated with respiratory problems in infancy, childhood [16] and adolescence [2]. Ramsay et al. [17] examined the effect of prenatal exposure to nicotine and alcohol on cortisol at two and six months of age. They [17] found that prenatal exposure to nicotine and alcohol was associated with a decreased cortisol response at two months of age, reflecting a trend toward higher cortisol levels. At this age, a non-vigorous cortisol response might be less than optimal [17]. This finding was not significant at six months of age, despite a *trend* for higher cortisol levels.

In the longer term, PTE is associated with childhood overweight [1] and obesity in adolescence [3], with an increased risk of cognitive problems [11], and it is also an independent risk factor for behavioral problems in the offspring of adolescents [7] and adults [25]. Wakschlag et al. [24], adjusting for covariates, found that young boys with PTE were likely to develop an earlier onset of delinquency. One mechanism highly suspected to underlie this relationship is alteration of the neuropsychological development, which may influence subsequent aggressiveness [10] and life-course persistent antisocial behavior [15]. Prenatal exposure of the fetal brain to nicotine may alter gene expression [21] and/or the developing nicotine receptors [6, 21].

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There are studies on the effect of PTE on the offspring of adult mothers [13] but, surprisingly, there is little recent research on the influence of PTE on infants born to teen mothers [22]. Maternal HPA axis during pregnancy is normally activated [4, 5]. Excessive glucocorticoids – beyond pregnancy hypercortisolism – may cross the placenta and induce elevated cortisol in fetal plasma. Tobacco smoke contains several harmful gases, including carbon monoxide and nicotine, which can readily cross the placenta and alter fetal HPA axis development. This may occur through vasoconstriction or via maternal malnutrition, reducing oxygen and nutritive elements reaching the fetal brain [8, 21].

This paper investigated whether PTE was associated with increased cortisol levels in infants of teen mothers. Young mothers in our sample are part of high-risk families including other factors than their young age (i.e., low income and educational levels, single motherhood, at risk for major depression (MD) and conduct disorder) [4]. In developing their full capacity of self-regulation, infants go through a normal bio-behavioral shift in their adrenocortical system around the age of four months [4]. This is why we examined cortisol at this age.

## Methods

The sample comprised of 212 infants of teen mothers (118 girls, 94 boys) who participated in a study described in details elsewhere [4]. All mothers were primiparous and were 17 years [standard deviation (SD) = 1.0] when they gave birth. They were mostly French-speaking Canadians (64%), some were English-speaking (8%) and some of other ethnolinguistic origins (28%). Infants were four months (M = 4.38, SD = 0.4), healthy at birth, with a body mass index (BMI) of 16.35 (SD = 2.45) at the time of study. Gestational age ranged from 38 to 42 weeks.

Saliva samples were collected at midmorning everyday to avoid circadian fluctuation, and immediately frozen at −18°C until analysis. Salivary cortisol concentrations were determined with a competitive solid-phase radioimmunoassay (RIA) (hydrocortisone, Compound F, Coat-A-Count, Diagnostic Products Corporation Company, Los Angeles, CA, USA). The cross-reactivity was 4.7%. The intra-assay coefficient of variation was 3%. Cortisol RIA randomly repeated were correlated ($r = 0.99$, $P < 0.001$).

A questionnaire was developed, for the purposes of the study, and administered to the mothers. This instrument asked about the type, frequency, and time of consumption of cigarettes and psychoactive drugs before and during each trimester of pregnancy. At about four months postpartum, we asked mothers about their postnatal consumption during a home visit. Of the 212 participants, 151 smoked during pregnancy. PTE was defined as prenatal exposure to at least one cigarette per week. About 20% of the participants smoked more than 100 cigarettes per week prior to pregnancy. After the initial data collection of this study began, some of the participants ($n = 53$) were administered parts of a computerized version of the National Institute of Mental Health Diagnostic Interview Schedule (NIMH-DIS) (CDIS Group, 1991–1992) to diagnose lifetime tobacco per nicotine dependence as well as lifetime history of MD. Forty-one percent (22 of 53) had a DIS diagnosis of lifetime tobacco dependence.

The study was approved by the Ethics Committee of the local institution. Mothers gave written informed consent. A research assistant visited them at home three times to assess PTE. The first visit took place during early pregnancy, the second at the end of the third trimester and the third at four months postpartum, when the mothers also answered questions on breastfeeding practice. Mothers and infants visited our laboratory, where infant salivary cortisol was collected twice, at 10:00 hours and an hour later. No infant was suffering from acute infection, pain, a chronic condition, or was taking any medication which might have influenced cortisol levels when saliva was collected.

First, *a priori* power calculation determined that, with the available sample size, we would have a power of $>0.90$ to detect a medium effect size. Second, we excluded two infants that were breastfed by mothers who reported using psychoactive drugs in order to avoid confounding effects (final sample = 212). Third, we conducted preliminary analyses of variance to test for potential confounding influences known from the earlier literature; namely birth weight, sex, milk ingestion, or nap in the car. Fourth, we used descriptive analysis to describe PTE. Finally, we used a propensity-score analysis, which adjusts for potential confounding factors, identified from the literature, and which minimizes the selection bias (of observational studies). Propensity score (PS) analysis is a robust technique which attempts to mimic the random assignment of a randomized clinical trial [19]. PSs were the estimated conditional probability that an infant will be assigned to the PTE group or not, given the vector of observed covariates. In a first step, we estimated PS for PTE group membership, by fitting a logistic regression model where the dependent variable was PTE-predicted probability. The independent variables were covariates previously identified as important: infant BMI, lifetime MD as assessed with DIS – a measure we used in our previous work [4] with teens who had no difficulty in answering the questions – and prenatal exposure to other substances. In a second step, we included PSs of PTE as a continuous covariate, in a repeated analysis of covariance with PTE as between-subjects factor and cortisol as within-subjects factor. We set significance as $P < 0.05$.

## Results

Regardless of PTE status, the infants' mean cortisol was 0.25 μg/dL (±SD = 0.17). Cortisol levels did not differ as a function of factors that could have influenced cortisol variability. There was no significant main effect, within-subjects effect, or interaction between PTE and cortisol levels, after controlling for PSs of PTE [$F(1, 151) = 0.95$, ns]. Mean cortisol levels of PTE infants vs. not-PTE infants were 0.24 (±0.17) and 0.25 (±0.16) μg/dL, respectively. After excluding a significant correlation between PTE and infant cortisol, we examined whether DIS lifetime diagnoses of tobacco dependence were associated with infant cortisol. Taking infant cortisol levels as within-subjects factor, RANOVA with lifetime tobacco dependence as the between-subjects factor indicated that tobacco dependence had no main effect on infant cortisol. Similarly, there were no differences in infant cortisol levels as a function of number of cigarettes smoked by mothers prior to pregnancy, as well as up to three months after giving birth. Finally, we compared cortisol levels of infants ($n = 52$) exposed to *both* nicotine and alcohol to those of infants in the rest of the sample [2]. There were no significant differences observed (0.27 vs. 0.24 μg/dL).

**Table 1** Report of number of smokers (%), mean number of cigarettes smoked per week (±SD), and prevalence (%) of multi-substance use before gestation and throughout the trimesters of pregnancy.

| Consumption | Before gestation | First trimester | Second trimester | Third trimester |
|---|---|---|---|---|
| Smokers (n=212) | 151 (71%) | 122 (57%)[a] | 122 (57%) | 122 (57%) |
| Cigarettes smoked/week | 79[b] (±76) | 31 (±4.00) | 33.5 (±2.86) | 30 (±2.92) |
| Other substance usage[c] | | | | |
| Alcohol | | | | |
| At lease once daily | 11 (5%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 1–3 times/week | 40 (19%) | 11 (5%) | 2 (1%) | 0 (0%) |
| 1 or twice/month | 95 (45%) | 49 (23%) | 39 (15%) | 25 (12%) |
| Once or none/year | 49 (31%) | 153 (72%) | 178 (84%) | 187 (88%) |
| Psychoactive drugs[d] | | | | |
| Daily | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Regular use | 38 (18%) | 6 (3%) | 0 (0%) | 2 (1%) |
| Occasional use | 89 (42%) | 38 (18%) | 8 (4%) | 6 (3%) |
| Abstinence | n/a | 167 (79%) | 203 (96%) | 203 (96%) |

Definitions: daily=every day, regular use=1–3 times/week, occasional use=once or twice/month, Abstainer=did not drink at all.
[a]Fourteen participants who smoked prior to pregnancy reported no cigarette smoking in pregnancy.
[b]About 20% of smokers reported smoking >100 cigarettes per week before pregnancy.
[c]About 25% of the sample used nicotine, alcohol, and drugs.
[d]Along with tobacco, marijuana was the most frequently reported psychoactive drug (35%).

## Discussion

We found no evidence of association between PTE and increased infant cortisol levels at four months of age. Our findings are at odds with Ramsay et al. [17] of higher cortisol levels in two-month-old infants prenatally exposed to nicotine and alcohol. At first glance, our null finding seems to indicate that the PTE influence may no longer be detectable by four months of age. This disagrees with Ramsay et al. [17] who reported a trend toward higher cortisol levels at six months. Nonetheless, our results concur with Jacobson et al. [12] that infant cortisol levels were not associated with prenatal exposure to marijuana and tobacco. Because maternal and fetal hormonal systems are interconnected, our data are intriguing, especially with a potential teratogen like tobacco.

A conservative explanation of our findings would be the use of the self-report questionnaire, which may have increased measurement error and/or social desirability bias. Furthermore, mothers did not report heavy smoking, and there seems to be a decreased consumption of tobacco throughout pregnancy. It is unclear whether this is a true decrease, or an influence of social desirability. Alternatively, any previous short-term effect of PTE (even with small smoking quantity) could have been overcome or diminished to the point of being undetectable at four months of age.

The study strengths include a prospective design, a large sample size ensuring statistical significance, and a reduction of the selection bias through rigorous analysis with propensity-score matching. However, our study presents two limitations. First, we used a self-report measure of PTE, thus under-reporting is likely. This limitation has been mitigated by our information on pre-pregnancy smoking data, however. Second, if we had obtained a measure of cortisol response, perhaps our findings would have been different. As a result, our data should be interpreted cautiously, because there was probably a restricted range in the reported quantity/frequency of smoking. This under-reporting could be genuine, or influenced in part by social desirability (which we did not control for).

Cortisol circadian rhythm may not be fully established for all the infants in a stable manner (4). This could have partly influenced our findings. Furthermore, a relation may exist between PTE and cortisol in the area under the curve, in the case of repeated hormonal measurements. However, the relationship between maternal smoking and infant cortisol levels has not been shown in other studies [9]. Future prospective research should monitor daily smoking, while including multiple infant cortisol samples. Studies could also benefit from biological validation of PTE, through such measures as salivary [13], urine, or meconium cotinine levels.

## Acknowledgments

This study was supported by post-doctoral fellowship awards to the first author from the Canadian Institutes of Health Research (CIHR) and Ontario Women's Health Council (OWHC) as well as by the Marjorie Young Bell Faculty Fund and the Mount Allison University New Faculty Start-up Grant. We thank the UHN Quality of Life Manuscript-Review Seminar members for their comments on the first draft, as well as Darren Mercer and Alberta Schaap for proofreading the final versions of this paper.

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The authors stated that there are no conflicts of interest regarding the publication of this article.

Received June 23, 2009. Revised May 14, 2010. Accepted May 25, 2010. Previously published online August 13, 2010.