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Associations of maternal prenatal smoking with umbilical cord blood hormones: the Project Viva cohort

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ABSTRACT

Background. Maternal smoking during pregnancy is associated with low fetal growth and adverse cardiometabolic health in offspring. However, hormonal pathways underlying these associations are unclear. Therefore, we examined maternal smoking habits and umbilical cord blood hormone profiles in a large, prospective cohort.

Methods. We studied 978 mother/infant pairs in Project Viva, a Boston-area cohort recruited 1999–2002. We categorized mothers as early pregnancy smokers, former smokers, or never smokers. Outcomes were cord blood concentrations of IGF-1, IGF-2, IGFBP-3, leptin, adiponectin, insulin, and C-peptide. We used linear regression models adjusted for maternal pre-pregnancy body mass index (BMI), race/ethnicity, parity, education, and infant sex. We conducted analyses in the full cohort and stratified by infant sex.

Results. Thirteen percent of women were early pregnancy smokers, 20% former smokers, and 68% never smokers. Infants of early pregnancy smokers had lower IGF-1 adjusted for IGFBP-3 [−5.2 ng/mL (95% CI: −8.6, −1.7)], with more pronounced associations in girls [−10.7 ng/mL (95% CI: −18.5, −2.9) vs. −4.0 ng/mL (95% CI: −8.4, 0.4) for boys]. Early pregnancy smoking was not associated with cord blood hormones other than IGF-1. Infants of former smokers had a cord blood hormone profile similar to infants of never smokers.

Conclusions. As compared to mothers who never smoked, early pregnancy smokers had infants with lower cord blood IGF-1 which could prime adverse metabolic outcomes. This provides further reason to support smoking cessation programs in women of reproductive age.

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; IGF-1, insulin-like growth factor-1; IGF-2, insulin-like growth factor 2; IGFBP-3, insulin-like growth factor binding protein 3; SD, standard deviation.

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1. Introduction

Cigarette smoking continues to be a major public health threat. It is the leading preventable cause of death in the United States and was estimated to have caused over 7 million deaths globally in 2015 [1]. Maternal smoking during pregnancy has been consistently associated with offspring morbidity, including lower birth weight by 175–200 g [2] and childhood adiposity and insulin resistance [3,4].

Prenatal exposure to nicotine, a major component of cigarette smoke, reduces placental blood flow which leads to fetal hypoxia and low fetal growth [5]. Similarly, rodents prenatally exposed to nicotine develop greater adiposity and abnormal glucose homeostasis in adulthood [6]. However, the hormonal pathways through which nicotine or other components of cigarette smoke may lead to these metabolic health outcomes are unclear.

Examining the extent to which prenatal smoking is associated with the umbilical cord blood hormonal milieu may provide additional insight into potential pathways of action. Lower concentrations of cord blood growth factors, particularly insulin-like growth factor-1 (IGF-1), are associated with smaller size at birth [7]. Lower cord blood adipokines, leptin and adiponectin, have been associated with early life weight gain [8]. Also, higher cord blood insulin has been associated with higher plasma insulin in early childhood which may have implications for development of insulin resistance in later life [9].

Although there have been several prior studies of prenatal smoking and metabolic cord blood hormones [10–22], these typically assessed only IGF-1 or adipokines, often did not account for potentially important confounding variables like socioeconomic status, and frequently included small sample sizes ($n \leq 150$). Also, only one prior study included women who were former smokers [17], and none have evaluated sex-specific associations, despite growing evidence that prenatal toxic exposures including smoking may have sex-specific effects [23].

In the present analysis, we used data from a large, prospective cohort to examine the extent to which maternal smoking habits were associated with IGF-1, insulin-like growth factor 2 (IGF-2), insulin-like growth factor binding protein 3 (IGFBP-3), leptin, adiponectin, insulin, and C-peptide in cord blood. Based on known associations of prenatal smoking with low fetal growth and higher offspring adiposity and insulin resistance, we hypothesized that prenatal smoking would be associated with lower IGF-1, lower adipokines, and higher insulin and C-peptide in cord blood, and that associations would differ by infant sex.

2. Methods

2.1. Study Population and Design

From 1999 to 2002, we recruited pregnant women to the prospective cohort Project Viva during their first prenatal visit (median 9.9 weeks of gestation) at Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in eastern Massachusetts [24]. A total of 2128 women with a live singleton birth were included in the cohort. For the present analysis, we excluded 16 women with pre-existing type 1 or type 2 diabetes mellitus, 1124 women who did not have cord blood hormones measured, and 10 women without information on prenatal smoking status. We obtained cord blood only from about one-half of the total cohort because obstetric providers, whose primary focus was on clinical care, not research, were responsible for the blood collection, and because we collected cord blood at only one of the two main delivery hospitals. Women included (n = 978) in the present analysis versus excluded (n = 1150) were more likely to be white (70% vs. 63%), and their children were more likely to have a longer gestational length (mean 39.6 vs. 39.2 weeks) and greater birth weight for gestational age z-score (mean 0.24 vs. 0.11 units). Women included versus excluded had similar rates of smoking during early pregnancy (13% vs. 12%) (Supplementary Table 1). All women provided written informed consent, and Institutional Review Boards of participating institutions approved the study.

2.2. Measurement of Exposure

We collected data on maternal smoking habits during pregnancy based on self-report and categorized participants into three groups: (1) never smokers, (2) former smokers, and (3) early pregnancy smokers. At the time of study enrollment (median 9.9 weeks of gestation) we asked participants whether they had ever smoked, and women who smoked <100 cigarettes in their lifetime were categorized as "never smokers." Next, we asked women who smoked >100 cigarettes in their lifetime whether they had smoked in the 3 months before learning they were pregnant. We categorized women who stopped smoking 3 months or more before learning they were pregnant as "former smokers." We categorized women who smoked during the 3 months before learning they were pregnant or reported smoking on the first or second trimester questionnaire, during their delivery interview, or in their prenatal medial record as "early pregnancy smokers." Of 125 early pregnancy smokers, 72 smoked in the 3 months before learning they were pregnant and reported having quit by the time of the first trimester questionnaire (9.9 weeks gestation). We categorized these women as early pregnancy smokers because they may have smoked after the time of conception. We refer to all 125 women as "early pregnancy smokers" because the majority reported having quit by the end of the first trimester. This categorization is consistent with prior analyses in this cohort (e.g., [3]).

We also collected information about ongoing passive smoke exposure (hours per week at home, work, or in restaurants) on the first trimester questionnaire. We considered women to be exposed if they reported greater than or equal to 2 hours of passive smoke exposure per week.

2.3. Measurement of Outcome

The delivering obstetrician or midwife collected cord blood samples from the umbilical vein immediately after delivery. We refrigerated whole blood for less than 24 h, spun and