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Prenatal Tobacco Exposure, Biomarkers for Tobacco in Meconium, and Neonatal Growth Outcomes

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Abstract

Objective—To assess relationships between marker concentrations of tobacco in meconium and weekly self-reported maternal cigarette consumption, and prediction of neonatal growth outcomes.

Study design—Pregnant mothers (N=119) from a longitudinal maternal smoking and infant neurobehavioral study (BAM BAM) provided daily tobacco smoking histories. Nicotine, cotinine, and *trans*-3'-hydroxycotinine (OHCOT) concentrations were quantified in 111 neonatal meconium specimens by liquid chromatography-tandem mass spectrometry.

Results—Median self-reported 3rd trimester smoking was 5.9 cigarettes per day among smokers. Meconium samples from infants born to non-smokers (N=42) were negative for tobacco markers, even though specimens from self-reported smokers (N=41) were positive for (median, range) nicotine (50.1ng/g, 3.9–294), cotinine (73.9ng/g, 6.4–329), and OHCOT (124.5ng/g, 10.2–478). Quitters (N=28) self-reported stopping smoking in gestational weeks 2–39. Four meconium specimens from quitters were positive for tobacco biomarkers. Reduced birth weight, length and head circumference significantly correlated with presence of meconium markers, but not with individual or total marker concentrations. Among quitters and smokers, reduced infant birth weight, head circumference and gestational age correlated with total and average daily cigarette consumption in the 2nd and 3rd trimesters.

Conclusion—Smoking cessation or reduction during pregnancy improved neonatal outcomes. The window of detection for tobacco in meconium appears to be the 3rd trimester; however, low exposure in this trimester failed to be detected. These results will aid physicians in educating women who are pregnant or thinking about becoming pregnant on the negative consequences of smoking during pregnancy. In addition, infants at risk can be identified at birth to assist early intervention efforts.

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Keywords

Nicotine; Smoking; Meconium; Pregnancy; *In Utero* Drug Exposure

Despite strong public health warnings, 16.3% of women smoke tobacco throughout pregnancy.¹ *In utero* tobacco exposure is associated with decreased fetal growth, increased infant irritability and hypertonicity, alterations in brain structure or function, and increased risk of sudden infant death syndrome.^{2–5} Gestational tobacco exposure also is associated with deficits in cognitive function, and increased risk for behavioral disorders, attention deficit/hyperactivity disorder and tobacco dependence later in life.^{6–9}

Biological monitoring of maternal and neonatal specimens is a more objective measure of duration and intensity of *in utero* tobacco exposure than maternal self-report, as these accounts are subject to recall bias and social stigmas.^{10–11} Testing of meconium, which begins to form at the 13th gestational week,¹² is an advantageous neonatal matrix due to ease of collection, adequate specimen volume, and long window of drug detection;¹³ however, contribution from secondhand/environmental exposure is still unclear.^{14–15} In adults, nicotine is oxidized to cotinine and further metabolized to *trans*-3'-hydroxycotinine (OHCOT), primarily by CYP2A13 and CYP2A6.¹⁶

The aims of this study were to assess relationships between marker concentrations of tobacco in meconium and daily self-reported maternal cigarette consumption, and prediction of neonatal growth outcomes. There are limited studies of utilizing marker concentrations of tobacco in meconium, particularly those of nicotine and OHCOT, to validate maternal self-report and predict neonatal outcomes. A better understanding of the relationships between tobacco markers in meconium, maternal smoking, and neonatal outcomes is needed, as these data could identify children at risk and strengthen smoking cessation interventions during and following pregnancy.

Methods

Women were enrolled in the Behavior and Mood in Babies and Mothers (BAM BAM; PI: L.S.) study, a longitudinal study assessing effects of gestational tobacco exposure on infant neurobehavior. Recruiting was designed to oversample smokers to enroll smoking and non-smoking maternal cohorts. The study was approved by the Institutional Review Board of Women and Infants' Hospital (Providence, RI), and mothers provided written informed consent. Pregnant women ages 18–40 years were enrolled during the 3rd trimester and gave detailed daily tobacco intake information throughout pregnancy. Initial study visits occurred at 28 weeks, with 1–2 follow-up interviews at 34–38 weeks, and a perinatal interview at delivery. Self-reported cocaine or other illicit drug use other than cannabis was an exclusion. At each visit, trained interviewers recorded cigarettes smoked each day of pregnancy using the timeline follow-back methodology. Total and mean cigarettes smoked per day during each gestational week were calculated. Secondhand smoke exposure was assessed weekly with questions on mean weekly hours of exposure in and outside the home.¹⁷ Oral fluid specimens were collected by passive drool during the 3rd trimester and assayed for cotinine to provide additional biochemical verification of maternal smoking status.

Meconium specimens were collected within 72h of delivery by combining samples from multiple soiled diapers until appearance of milk stool. Meconium from multiple diapers was collected in a single polypropylene container and shipped frozen to the National Institute on Drug Abuse for analysis. Cotinine, nicotine and OHCOT concentrations were quantified in meconium by a validated liquid chromatography tandem mass spectrometry (LCMSMS)

method.¹⁸ LCMSMS limits of quantification (LOQ) were 2.5ng/g nicotine, 1.0ng/g cotinine, and 5.0ng/g OHCOT. This method also quantified opioids, methamphetamine, cocaine and several metabolites.¹⁸ A separate 2-dimensional gas chromatography mass spectrometry method quantified cannabinoids, Δ^9 -tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), 8 β ,11-dihydroxy-THC, cannabinol, and 11-nor-9-carboxy-THC (THCCOOH) in meconium.¹⁹ Oral fluid specimens were analyzed for cotinine by Salimetrics™ with an enzyme-linked immunosorbant assay with a LOQ of 0.15ng/mL.

Statistical calculations were with GraphPad Prism 5 and SPSS 16.0 for Windows. Normality was assessed with visual inspection of box plots and Kolmogorov–Smirnov tests. Non-parametric *t* tests evaluated differences between 2 groups and non-parametric one-way analysis of variance determined group differences between 3 or more groups. Pearson and Spearman correlations evaluated associations between normally and nonnormally distributed variables, respectively. Analysis of covariance and multiple regression models were employed to adjust for covariates. Statistical probability $P < 0.05$ was considered statistically significant for all comparisons.

Results

Criteria for study inclusion were met by 119 women: 46 (38.7%) denied smoking during pregnancy (“non-smokers”), 45 (37.8%) smoked throughout pregnancy (“smokers”) and 28 (23.5%) reported quitting prior to delivery (“quitters”). Meconium specimens from 111 infants were present in sufficient quantity for analysis.

Maternal and infant characteristics for each group are summarized in Table I. Significant group differences were seen for group percent with low socioeconomic status (SES) (based on a score of 4 or 5 on the Hollingshead Index, which assesses SES by evaluating parental social position including occupations and education of both parents)²⁰, and average secondhand smoke exposure >1h/day throughout pregnancy (Table I). Infant birth weight, length and head circumference were significantly different between nonsmokers, quitters and smokers, with the smokers’ infants having the lowest weight and shortest length and head circumference (Table I). Total trimester cigarettes smoked and average daily cigarettes smoked for self-reported quitters and smokers are shown in Table II. Mann-Whitney *t* tests indicated that all variables described in Table II were significantly different between quitters and smokers ($P < 0.0001$).

Meconium samples were negative (<LOQ) for all 3 tobacco markers from all self-reported non-smokers and positive for all self-reported smokers (women who continued to smoke until delivery) (Table II). Quitters (N=28) self-reported stopping smoking in gestational weeks 2–39. Only 4 meconium specimens from infants born to quitters were positive for tobacco biomarkers. These mothers reportedly quit smoking during gestational weeks 9, 12, 16 and 39. Median concentrations of meconium in the 4 positive quitter specimens (nicotine 4.3ng/g, cotinine 4.4ng/g, and OHCOT 20.6ng/g) were 5–15 times lower than those in smokers’ meconium (Table II). Quitters also smoked 2–9 times fewer cigarettes/day throughout pregnancy than smokers (Table II).

Oral fluid cotinine measurements verified or refuted maternal self-reported smoking behavior. Self-reported quitters with negative meconium all had 3rd trimester oral fluid specimens that verified maternal self-report. In these women, oral fluid cotinine was <6.5ng/mL, except for a single oral fluid sample from a week-33 quitter taken 10 weeks prior to delivery with cotinine present at 18.7ng/mL; these results are consistent with maternal self-report.

Self-reported quitters with positive meconium reportedly quit smoking during gestational weeks 9, 12, 16 and 39; however, 3rd trimester oral fluid specimens were positive for weeks 9 and 16 quitters, suggesting continued smoking (Table III). For both of these women, oral fluid cotinine measurements were taken 1 and 2 months prior to delivery and ranged from 32.6–103.6ng/mL for the self-reported week 9 quitter and 13.2–23.7ng/mL for the self-reported week 16 quitter. The positive oral fluid results, and positive meconium, indicate these women continued smoking into the third trimester. A single oral fluid sample taken from the week 12 quitter 2 months prior to delivery was negative for cotinine (<LOQ, 0.15ng/mL), although meconium from this mother's infant contained 30ng/g OHCOT. Oral fluid specimens from the week 39 (2 weeks prior to delivery) quitter taken at 1 and 2 months and 19 d prior to delivery ranged from 9.9–42.5ng/mL cotinine (Table III).

All third trimester oral fluid specimens from self-reported non-smokers contained less than 1.5ng/mL cotinine, well-below the suggested 10ng/mL cutoff to differentiate smokers from non-smokers.²¹ For smokers, all oral fluid specimens collected in the 3rd trimester were positive for cotinine with concentrations ranging from 2.1–439.8ng/mL and every woman had at least 1 oral fluid specimen positive above the 10ng/mL cutoff. Among quitters and smokers, 3rd trimester oral fluid concentrations of cotinine were strongly correlated (ρ values ranged from 0.776–0.871, all P values <0.0001) with concentrations in meconium (nicotine, cotinine, OHCOT and total) and total and average daily cigarette consumption in the 3rd trimester.

Infant birth weight, length and head circumference significantly correlated with the presence, but not concentrations, of 1 or more meconium markers, after adjusting for low SES, and maternal age, income and highest education completed (Table IV). These covariates were chosen as they may affect infant growth outcomes or maternal access to prenatal care. A trend was seen between gestational age and meconium positivity ($P=0.076$). There were no significant correlations between nicotine, cotinine, OHCOT or total concentrations in meconium and infant growth outcomes of weight, length, age and head circumference, with or without adjusting for covariates (ρ values –0.167–0.247, all P values >0.10). Although no significant differences were observed in neonatal growth outcomes between 1st, 2nd and 3rd trimester quitters (P values >0.50), neonatal outcomes of quitters' infants, regardless of maternal quit date, were significantly different from smokers' infants and no different from nonsmokers' infants, when adjusting for covariates of low SES, and maternal age, income and highest education completed (Table I).

Among quitters and smokers, concentrations (nicotine, cotinine, OH-COT and total) in meconium correlated strongly to self-reported total and average daily cigarette consumption in the 2nd and 3rd trimesters (ρ values 0.320–0.567, P values <0.0001–0.031). Also, among quitters and smokers, reduced infant birth weight, head circumference and gestational age correlated with average daily (P values <0.001–0.014; standardized β s ranged from –5.13 to –2.52) and total cigarettes smoked in the 3rd trimester (P values <0.001–0.024; β s ranged from –5.03 to –2.26), when adjusting for covariates. Reduced infant birth length was predicted by mean daily cigarettes smoked in the 3rd trimester ($P=0.045$, $\beta=-1.80$), however, only a trend was seen with total cigarettes smoked in the 3rd trimester ($P=0.075$, $\beta=-1.80$).

Cannabinoids were detected in 5 meconium specimens from smokers. All 5 specimens were positive for THCCOOH from 12.2–411ng/g. Two specimens, with the highest THCCOOH concentrations (90.9 and 411ng/g), also were positive for cannabinol and 8 β ,11-dihydroxy-THC with concentrations ranging from 19.9–48.5ng/g and 21.0–24.6ng/g, respectively. Three women with cannabinoid positive meconium denied smoking cannabis during pregnancy; the other 2 women reported low cannabis intake (4–6 joints over the course of

their pregnancies), with use prior to week 15, inconsistent with meconium findings. In total, 24 participants self-reported cannabis smoking ranging from 0.2–215.5 cannabis cigarettes smoked throughout pregnancy. All meconium specimens were negative for cocaine, amphetamine, methadone and buprenorphine metabolites.¹⁸

Discussion

Adverse obstetrical and neonatal outcomes, including preterm delivery, low birth weight, fetal growth restriction, placenta abruption and previa, often result from tobacco consumption during pregnancy.⁴ Adverse infant birth outcomes following tobacco exposure are as significant as those from illicit drug exposure.²² *In utero* tobacco exposure also is associated with cognitive deficits, behavioral problems and tobacco dependence in adulthood.^{6–9} Therefore, it is critical to identify *in utero* tobacco exposure with the aim of reducing gestational exposure during the present and future pregnancies, offering supportive services to exposed infants and cessation therapy to mothers, and further minimizing tobacco exposure in the home after pregnancy to improve infant and childhood development.

The relationships between marker concentrations of tobacco in meconium and neonatal outcomes are unclear. Two studies demonstrate a dose-effect relationship between infant birth weight and marker concentrations of tobacco in meconium,^{15, 23} although further data by ourselves and others refuted this relationship.^{2, 14, 24} In the present cohort, no significant relationship was observed between infant growth outcomes (age, weight, length and head circumference) and meconium nicotine, cotinine, OHCOT and total marker concentrations. However, this investigation demonstrates a significant relationship between the presence of 1 or more meconium nicotine markers and infant, birth weight, length and head circumference, with a trend seen for gestational age (Table IV). Similar findings were reported by Gray et al for gestational age, birth weight and head circumference.^{2, 14} Our data showed that infants of quitters, regardless of quit date, had growth outcomes similar to infants from nonsmoking women, and were significantly different from infants born to mothers who continued to smoke during pregnancy, after adjusting for low SES and maternal age, income and education (Table I).

We showed that meconium positive for tobacco marker(s) predicts infant outcomes, and that marker concentrations for tobacco in meconium are correlated with total tobacco exposure. However, marker concentrations for tobacco in meconium did not predict severity of neonatal effects. Sherif et al²³ showed a negative correlation between birth weight and cotinine concentrations in meconium; however, our data and others^{2, 14, 25} more recently showed relationships only with positivity of meconium or categorically high (95th percentile) concentrations and poor infant outcomes. More research is needed on timing of maternal quitting of tobacco smoking and effects on infant outcomes.

All meconium specimens from smokers were positive for all 3 tobacco markers. Previously, we found that adding nicotine and OHCOT tobacco markers identified 27% more tobacco-exposed infants.¹⁴ Braun et al reported similar results, with a 10% increase in detection.¹⁵ In our cohort, all but 1 positive meconium specimen contained cotinine and all but 2 specimens were positive for nicotine. Inclusion of OHCOT (30.3ng/g) additionally identified smoking in one 12-week tobacco quitter.

It was surprising that more meconium samples from tobacco quitters were not positive; 3 of 4 specimens from self-reported 3rd trimester quitters (quit weeks 29–33) were negative for all tobacco markers even with low LOQs. The 33-week quitter smoked 244 cigarettes during the 3rd trimester, or 2.5 cigarettes/day. The 30-week quitter smoked 29 cigarettes in the 3rd

trimester. The 29-week quitter (11 weeks prior to delivery) only smoked once during the 3rd trimester and had several month-long cessation periods during pregnancy. Oral fluid cotinine from the 29- and 30-week quitters taken during self-reported cessation were <10ng/mL; oral fluid cotinine 2.5 months prior to delivery from the 33-week quitter was 18.7ng/mL. These oral fluid data verify self-report.

Low detection of markers of tobacco in meconium among quitters may be explained by the exponential meconium accumulation model suggesting that nearly 80% of meconium accumulates after the 38th gestational week.²⁶ Similar findings from early 3rd trimester quitters were reported by Gray et al.² Among 6 women who reportedly quit smoking at least 1 month (30–73 days) prior to delivery, only 2 meconium specimens were positive for tobacco markers. Also in this cohort, among 55 self-reported smokers who continued smoking within 2 weeks of delivery, 5 infants had negative meconium; these women reported smoking 6–321 cigarettes in the 3rd trimester (0.1–3.1 cigarettes daily).² The relationship between marker concentrations for tobacco in meconium and the time interval from smoking cessation to birth is still unclear.

Clearly there is value in classifying exposed children based on self-report and meconium and oral fluid testing. Oral fluid and meconium analyses can identify unreliable maternal self-report and improve correct classification of a mother's smoking behavior. Three self-reported 1st or 2nd trimester quitters with positive infant meconium had 3rd trimester oral cotinine measurements >10ng/mL indicating likely active smoking,^{21, 27} as cotinine has a serum and oral fluid half-life of 17 hours.²⁷ Our data demonstrate that 3rd trimester oral fluid cotinine analysis is an additional indicator of active maternal smoking.

Interestingly, one mother who self-reported quitting in week 12 had an infant who was positive for meconium (30ng/g OHCOT only) and a single oral fluid sample taken 2 months prior to delivery was negative for cotinine (<LOQ). One explanation for this finding is that the woman continued to smoke beyond the self-reported quit date and abstained from smoking just prior to the single oral fluid cotinine measurement. Meconium is thought to reflect 2nd and 3rd trimester fetal exposure, although our data for multiple drug analytes suggest meconium only reliably detects 3rd trimester intake.^{2, 28} Although it is unlikely that this meconium specimen reflects fetal exposure to tobacco prior to gestational week 12, this possibility cannot be excluded. Another reason for this positive meconium finding may be maternal second hand exposure to tobacco smoke not detectable with a single oral fluid sample.

This study evaluated relationships between total or mean 3rd trimester cigarettes/day and multiple marker concentrations of tobacco in meconium.^{2, 29} Similar to previous findings, we document a dose-concentration relationship between increasing marker concentrations for tobacco in meconium and higher mean daily and total cigarettes smoked during the 3rd trimester. This study's assessment of tobacco smoking behavior during pregnancy with weekly prospective collection of total and average cigarettes smoked per day is more thorough than most previous studies. However, the poor correlation coefficients seen in previous studies, as well as ours, indicate that it is inappropriate to predict number of cigarettes smoked from a specific marker concentration in meconium. Also, number of cigarettes smoked does not account for variability in smoking topography including number of puffs, puff duration, depth of inhalation, breath hold time and spacing between puffs.

A strength of this investigation was assessment of polydrug exposure with selected analytical meconium methods; most studies assessing gestational tobacco exposure impact failed to evaluate this potential confounder. Although cannabinoid exposure during pregnancy may also lead to deficits in neonatal growth outcomes,³⁰ our study population

had few reports of cannabis use and only 5 cannabinoid positive meconium specimens, suggesting little contribution to outcomes by concurrent gestational cannabis exposure.

In summary, self-reported maternal tobacco consumption significantly correlated with marker concentrations for tobacco in meconium and the presence of 1 or more markers was significantly associated with decreased infant birth weight, length and head circumference. Infants of quitters, regardless of quit date, had growth outcomes similar to infants of non-smokers and significantly better than infants of smokers. These results support smoking cessation at any time during pregnancy may improve neonatal outcomes. This information may aid physicians in educating women who are pregnant or thinking about becoming pregnant on the negative consequences of smoking during pregnancy, and the consequences of environmental tobacco smoke for all children in the home. In addition, infants at risk can be identified at birth to assist early intervention efforts.

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Abbreviation List

OHCOT	<i>trans</i> -3'-hydroxycotinine
LCMSMS	liquid chromatography-tandem mass spectrometry
LOQ	limit of quantification
THC	Δ^9 -tetrahydrocannabinol
THCCOOH	11-nor-9-carboxy-THC

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Table 1

Maternal demographics and neonatal characteristics for 119 women classified by self-reported tobacco smoking status

	Non-Smokers N=46	Quitters N=28	Smokers N=45	P value
Maternal Characteristics				
Maternal Age	25.4 ± 5.5 yrs	23.6 ± 4.4 yrs	25.1 ± 4.1 yrs	0.264
mean ± SD (range)	(18–40)	(18–35)	(18–35)	
Gravida	2.6 ± 1.5	2.8 ± 1.9	3.3 ± 2.2	0.290
mean ± SD (range)	(1–7)	(1–8)	(1–12)	
Para, mean ± SD (range)	1.3 ± 1.1 (0–5)	1.3 ± 1.8 (0–7)	1.7 ± 1.6 (0–6)	0.341
Low Socioeconomic Status (%)	22.2%	35.7%	60.0%	0.001 ^a
Average Alcoholic	0.5 ± 0.8	1.1 ± 3.0	2.8 ± 6.2	0.104
Drinks/Month Throughout	(0–3.7)	(0–19.7)	(0–32.2)	
Pregnancy, mean ± SD (range)				
Secondhand Smoke Exposure (% , >1h exposure/day)	8.7%	50.0%	66.6%	< 0.0001 ^b
Infant Characteristics				
Infant Gestational Age	39.7 ± 1.3 wks	39.7 ± 1.3 wks	39.1 ± 1.6 wks	0.299
mean ± SD (range)	(36.0–41.6)	(36.9–41.9)	(33.4–41.6)	
Infant Weight	3464.1 ± 444 g	3556.9 ± 504 g	3162.5 ± 434 g	0.004 ^c
mean ± SD (range)	(2110–4340)	(2565–4525)	(1860–4025)	
Infant Length	51.0 ± 2.4 cm	51.5 ± 1.9 cm	49.2 ± 2.4 cm	0.005 ^c
mean ± SD (range)	(46.4–55.2)	(48.0–55.9)	(44.0–53.5)	
Infant Head Circumference	34.4 ± 1.3 cm	34.9 ± 1.7 cm	33.7 ± 1.5 cm	0.007 ^c
mean ± SD (range)	(32.0–36.8)	(32.0–37.0)	(29.5–36.6)	
1-min Apgar Score median (range)	8 (2–9)	8 (4–9)	8 (3–9)	0.916
5-min Apgar Score median (range)	9 (8–10)	9 (7–9)	9 (8–10)	0.489

^a A significant difference between non-smokers and smokers was demonstrated by post-hoc tests.

^b Post-hoc tests indicate a significant difference between non-smokers and smokers, and nonsmokers and quitters.

^c A significant difference between non-smokers and smokers, and quitters and smokers is seen for these variables following post-hoc tests.

Table 2

Median (range) self-reported tobacco use and marker concentrations for tobacco in meconium in self-reported smokers and quitters

	Quitters N=28	Smokers N=45
Quit Week ^a	13.5 (2–39) wks	N/A
Total Cigarettes Smoked ^b		
Trimester 1	414 (7–1470) n=28	850 (168–3120)
Trimester 2	55 (16–382) n=13	686 (93–2230)
Trimester 3	54 (0.1–244) n=6	548 (65–1880)
Average Cigarettes/Day ^b		
Trimester 1	4.7 (0.1–17.5) n=28	10.1 (2.9–37.1)
Trimester 2	0.8 (0.2–3.9) n=13	7.0 (0.9–22.8)
Trimester 3	0.9 (0.3–2.5) n=6	5.9 (1.7–20.0)
Meconium Concentrations (ng/g)	N=4 ^c	N=41
Nicotine	4.3 (<LOQ–37.0)	50.1 (3.9–294.0)
Cotinine	4.4 (<LOQ–18.0)	73.9 (6.4–329.0)
<i>trans</i> -3'-hydroxycotinine	20.6 (7.5–30.3)	124.5 (10.2–478.0)

^aQuit Week is defined as the first week that self-report data indicated zero cigarettes smoked followed by consecutive weeks until birth of zero cigarettes smoked.

^bData for quitters reflects only women who were smoking in the given trimester; women who had zero cigarettes smoked in a given trimester(s) were excluded from median calculations.

^cOnly data from the 4 positive meconium specimens from quitters are shown. Total N=24.

Table 3

Oral fluid and concentrations in meconium of the 4 self-reported quitters with positive meconium findings

	Nicotine in meconium (ng/g)	Cotinine in meconium (ng/g)	<i>Trans</i> -3'- hydroxycotinine in meconium (ng/g)	3 rd Trimester Oral Fluid Cotinine (ng/mL)
Week 9 Quitter	8.5	7.4	30	32.6–103.6 (n=2)
Week 12 Quitter	<LOQ	<LOQ	30	<LOQ (n=1)
Week 16 Quitter	37	18	11	13.2–23.7 (n=2)
Week 39 Quitter	<LOQ	1.5	7.5	9.9–42.5 (n=3)

Table 4 Mean $\pm$ SD (range) presence of biomarker tobacco in meconium and infant growth variables

Infant Characteristics	Negative Meconium	Positive Meconium	<i>P</i>
Estimated Gestational Age (weeks)	39.7 $\pm$ 1.2 (36.0–41.9)	39.2 $\pm$ 1.3 (36.1–41.6)	0.076
Birth Weight (g)	3497 $\pm$ 436 (2110–4525)	3198 $\pm$ 410 (2515–4230)	<0.001
Length (cm)	51.1 $\pm$ 2.1 (46.4–54.6)	49.5 $\pm$ 1.9 (45–53.5)	0.001
Head Circumference (cm)	34.9 $\pm$ 1.5 (32.0–37.0)	34.0 $\pm$ 1.4 (31.0–37.0)	0.003