Relationship between Self-Reported Maternal Tobacco Usage, Cotinine Levels and Birth Outcomes

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Abstract

Introduction: To ascertain the benefit of adding urinary cotinine testing to self-reported tobacco use in identifying tobacco use among pregnant patients and associations with birth outcomes.

Methods: Retrospective analysis of patients receiving prenatal care (01/01/2012–03/31/2013). Birth outcomes included independent variables and a composite: “poor outcome,” defined as any of the following: small for gestational age, low birth weight (LBW) (<2500 grams), or pre-term birth (PTB) (<37 weeks).

Results: Clinic patients receiving prenatal care with live births comprised study population (n=469). There was significant agreement between cotinine and self-reported usage (Kappa 0.76, p<0.001). While 211 patients had a positive cotinine assays (≥500 ng/mL) and reported tobacco use (true positive), 202 had a negative cotinine assay and reported no tobacco use (true negative); (sensitivity: 87.2%, specificity: 89.0%). Poor outcome was found in 25.0% (59/236) patients with positive cotinine assays versus 14.2% (33/233) with negative (p=0.004) and 23.6% (57/242) patients with self-reported use versus 15.4% (35/227) non-use (p=0.028). Newborn measurements were significantly smaller with tobacco use identified by either method. However, cotinine had associations with LBW and PTB univariately.

Conclusion: There was good agreement between cotinine testing and self-report of tobacco use. However, cotinine testing had additional associations with adverse birth outcomes.
Introduction

The detrimental effects of nicotine consumption during pregnancy are well-established in the literature. Tobacco use has been demonstrated to cause significant changes within maternal and fetal cell transcriptomes involved in the deregulation of numerous biological processes important for growth and development.\(^1\) It also results in statistically significant reductions of placental vascularization.\(^2\) Both of these findings are related to subsequent fetal morbidities such as small for gestational age infants (SGA), intrauterine growth retardation (IUGR) and low birth weight.\(^3-8\) Smoking includes additional increased risks for the following: cryptorchism in males,\(^9\) orofacial clefts,\(^10\) asthma and bronchopulmonary hyperreactivity,\(^11,12\) placental abruption,\(^13\) fetal malpresentation,\(^14\) preterm birth\(^15-16\) and stillbirth.\(^17-18\)

Various perinatal outcome variables have been examined and various conclusions have been drawn regarding the gestational age by which tobacco use should stop to ameliorate its deleterious effects.\(^19\) Researchers examining the effects of smoking cessation during pregnancy concluded that pregnant women who quit during their first trimester had reductions in the proportion of preterm deliveries and low birth weight infants.\(^20\) Another study concluded that maternal third-trimester cigarette use is a strong and independent predictor of birth weight percentile.\(^21\) In examining growth retardation with tobacco exposure, Horta et al. noted that there is a direct dose–response association.\(^7\) It was concluded in another study that if patients stop smoking before 20 weeks, the effects of tobacco may be ameliorated and the fetus will experience normal growth.\(^19\) Further, patients with a previous history of tobacco use with a previous child with intrauterine growth restriction may have normal fetal growth and normal birth weight for their current tobacco free pregnancy.\(^22\) These findings support continued attempts to influence patients to stop smoking even into the mid-trimesters of gestation.

The threshold of 8 cigarettes for heavy smoking in previous work by our clinic was chosen based on the finding in Kendrick’s 1995 review article from Cochrane Database published in 2008. Kendrick et al. 1995 concluded that a reduction in smoking to fewer than eight cigarettes a day is necessary to avoid reduction in infant birth weight.\(^23\) We found that even a modest reduction to <8 cigarettes per day in heavy smoking patients (defined as >8 cigarettes/day in our previous study) resulted in fewer preterm deliveries with a two-fold risk reduction in preterm birth. Our findings have important clinical impact on those who provide care to “at risk” populations showing, that, by identifying smokers and offering cessation/reduction programs significant reductions in preterm birth, IUGR, and tobacco associated complications may be reduced and/or avoided.
At prenatal screenings, patients are often asked in their medical history if they use tobacco. However, self-reported tobacco consumption may not be a reliable indicator of total exposure.\textsuperscript{24-25} Another alternative involves the major nicotine metabolite, cotinine, which has a half-life of around 16 hr, providing a means of assessing tobacco use over a 3 to 4–day period.\textsuperscript{26} Cotinine testing can be performed on saliva, urine or blood samples. In addition, studies have shown discrepancy between self-reports of tobacco use and cotinine levels.\textsuperscript{27-34} A study by Mathai et al. revealed that low birth weights due to smoking have greater correlation with urinary cotinine values than self-reports of tobacco use: “active maternal smoking was associated with a decrease in birth-weight of 12 g for every cigarette smoked in a day while there was a decrease of 25 g in birth-weight for every microgram of cotinine/mg of urinary creatinine.”\textsuperscript{34} These values could reveal more information regarding tobacco consumption, which is important to know in the context of pregnancy when studies have noted that there is a direct dose-response association between growth retardation and tobacco exposure.\textsuperscript{7} Does adding universal cotinine testing to the prenatal regimen, provide a benefit to providers who already have self-reported tobacco usage in the context of a smoking cessation program for pregnant patients? The purpose of this study is compare these two methods of determining tobacco use (urine cotinine screening and self-reporting) and their associations with birth outcomes.

**Methods**

Our study was approved by the Charleston Area Medical Center/West Virginia University institutional review board (IRB). This study is a retrospective review of existing medical records and a smoking cessation program surveys of pregnant patients at an obstetrics clinic at Charleston Area Medical Center Women’s and Children’s tertiary medical center who had urine substance screening completed between 01/01/12 and 03/21/2013. Prenatal care included universal urine drug screening at the initial obstetrical visit for all clinic patients with urine cotinine testing for tobacco us recently added to a patient’s initial prenatal visit. The overwhelming majority of our patients undergo their initial prenatal visit in the first trimester prior to 12 weeks gestation. Prior to attending an initial prenatal care appointment in the clinic, patients participated in an educational introduction to prenatal care class. This class explained the clinic’s policy on universal urine screening for alcohol, tobacco, and drug use. During the initial prenatal visit, patients were asked about tobacco, alcohol, and drug use during their medical history. During prenatal care, patients were asked by nursing staff if they were currently using tobacco during this pregnancy as part of a smoking cessation program.
Responses were recorded both in the medial record including the number of cigarettes smoked and on a scannable data sheet for the smoking cessation program. At each subsequent visit, smokers were asked again about their smoking status and amount consumed. In addition, urine was collected and sent for analyses. The clinic used Ameritox® Corporation to complete the drug screens, which included cotinine concentration testing. The assay had 95% sensitivity for cotinine with a lower limit of 34 ng/mL (Thermo Scientific DRI® Cotinine Assay) with a cut-off value at 500 ng/mL. In addition, as part of the clinic’s tobacco cessation program, clinic staff provided a tobacco use assessment surveys that asked the use of tobacco when the patient found out she was pregnant. Finally, the medical staff addressed tobacco usage at each obstetrical clinic visit assessing the patient’s willingness to quit or decrease.

Patient medical records were reviewed to abstract variables for the research study with multiple gestations and fetal anomalies excluded from analysis due to a priori increased risk for preterm delivery and adverse outcomes. We tested cotinine (positive vs. negative) and self-report (yes vs. no) groups of tobacco use with birth outcomes. Birth outcome data included head circumference, birth length, birth weight, NICU admission, congenital anomalies, small for gestational age (SGA), low birth weight (LBW) (<2500 grams), and preterm birth (PTB) (<37 weeks). Small for gestational age (SGA) was defined in our study as < 10% estimated fetal weight for gestational age by ultrasound. Poor fetal outcome was defined as having one or more of the following: SGA, LBW, or PTB. Data were analyzed by Spearman’s Rho, t-test for continuous variables and Chi-square for categorical variables, and an alpha of 0.05 for statistical significance. The software used for statistical analysis was Excel and IBM SPSS Statistics 19.

Results

The study population (n=469) included patients with both prenatal care in our clinic and birth at our hospital. The mean maternal age was 25.68 ±5.66 years with a predominately White population (79.3%). Maternal demographic characteristics of our study population are summarized in Table 1. Detection of illicit drug among the pregnant population was 25.8% and alcohol use 7.4%. The cotinine drug screen resulted in 233 (48.7%) patients with a negative assay (<500 ng/mL) and 236 (50.3%) patients with a positive cotinine assay (≥500 ng/mL). The mean cotinine value was 758.8 ±810.5 ng/mL. There was a moderate positive correlation between self-reported cigarette consumption and cotinine levels (R=0.71, p<0.001). We were able to collect the amount of tobacco used for all patients. Since consumption consisted of
cigarettes only, this was indicated in number of cigarettes consumed per day. The responses ranged from 1-40 cigarettes and on average these women smoked about a half-pack a day (10.6 ±6.74 cigarettes/day). We cross-tabulated the self-reported group and cotinine results group and found that the urine drug test for cotinine had a sensitivity of 87.2% and a specificity of 89.0%. There were 211 true positives and 202 true negatives. There were 25 (10.7%) false negatives (“not a smoker” but ≥500 ng/mL) and 31 (13.1%) false positives (“smoker” but <500 ng/mL).

All of the newborn measurements (head circumference, birth weight and birth length) were significantly smaller when mothers used tobacco (either identified by cotinine values or by self-reported usage (See Table 3 for details). There was also a small negative correlation between newborn measurements and cotinine levels, head circumference (R=−0.170), birth length (R=−0.208), birthweight (R=−0.222), all p<0.001. Poor fetal outcome was found in 25.0% (59/236) patients with positive continue assays (versus negative) 14.2%; p=0.004. For self-reported use, 23.6% (57/242) of those who stated they use tobacco had a poor outcome vs. those not reporting use: 15.4%; 35/227; p=0.028. However, in terms of LBW and PTB, only the higher cotinine levels (≥500 ng/mL) rather than self-reported usage were significantly associated.

Discussion

Our study found good agreement between cotinine levels and self-reported tobacco use. This suggests that our patients are forthcoming about their tobacco consumption and the self-report method does provide a representative measurement of tobacco use. In fact our specificity is higher than Britton’s but less than the findings reported with Burstyn. Overall, our study reports the best sensitivity and specificity rates. We think this may be due to the fact that there are overall high rates of smoking in West Virginia and that it is culturally acceptable to smoke while pregnant. The public awareness campaigns to raise awareness of the harmful effects of tobacco that have helped decrease the rates of smoking while pregnant in other states have not resonated in West Virginia.

Our urine cotinine findings confirmed studies in which there was a concordance between urinary cotinine levels and self-reported tobacco use. In fact, we found similar findings with a study by Wang et al. in that infant weight, length and head circumference had a significant exposure-response with cotinine levels but it was less clear with self-reported usage. Others have concluded that a combination of both urine cotinine testing and self-report cigarette use
could improve the effectiveness of the smoking cessation program.\textsuperscript{41} Because there were patients who reported no tobacco use, but had cotinine levels $\geq 500$ ng/mL, the drug test should be included in the prenatal visits to identify additional at-risk patients. Since cotinine levels were only collected at first prenatal visit, additional testing throughout the course of prenatal care might change our results. The urine cotinine testing allowed us to identify two groups of smokers: those who alleged they were not smoking but still positive for cotinine and those who admitted to smoking but were negative for cotinine. Each group represented a small, but significant number of our patients. We had 10.7\% false negatives (i.e. “self-reported non-smoker” with positive cotinine testing present) and 13.1\% false positives (i.e. “self-reported smoker” but negative cotinine testing) all whom could have enhanced counseling offered. The patients who were positive for cotinine could be gently urged to quit tobacco since they now had objective evidence they were still using nicotine. Those who admitted to smoking but had a negative test could be re-counseled to ascertain if they really were beginning to quit smoking (hence the negative testing) versus the issue of rapid clearance or effects of hydration on cotinine levels in some individuals.

Repeated cotinine testing may be a useful tool in counseling patients in tobacco risk reduction with goals set to decrease the levels. While decreasing a specific number of cigarettes may seem more tangible, cigarettes are a visual of what is seen outside the body and a cotinine level may be viewed as the effect of cigarette smoking. Thus, adding the cotinine test may provide clinicians with more ways to counsel their patients about the risks associated with substance use. During the past five years, our cumulative smoking cessation rate in the clinic was 16.3\%, resulting in almost 400 women achieving abstinence.

Finally, implementation of our screening program for tobacco cessation with urine cotinine testing might result in significant cost savings. Our urine cotinine screening cost us $10 per sample screened with a total of 469 screens done for this cohort of patients with a total cost of $4,690 per year. In our previous publication, we noted that by decreasing tobacco use to $<8$ cigarettes per day we prevented 3 preterm births $<32$ weeks at a cost of approximately $28,000 per delivery for a total savings of roughly $84,000 of NICU costs for these 3 preterm deliveries at $<32$ weeks.\textsuperscript{42} This amounts to an almost 18 fold cost advantage with the use of a single screen ($84,000/$4,980). Significantly more savings could be realized in the prevention of even earlier preterm deliveries below 32 weeks (see Table 4-attached separately for details). Even if there was a conservative 10\% reduction of preterm delivery rates with tobacco/cessation reduction programs with urine cotinine screening, the savings nationally in the United States
could be an astounding $205 million per year for deliveries <28 weeks and over $150 million per year for deliveries ≥28 to ≤32 weeks. Therefore, urinary cotinine screening to identify smokers remains significantly cost effective with even small reductions in preterm deliveries below 32 weeks.

More importantly, combining self-reported tobacco questionnaires and urine cotinine testing to improve smoking cessation rates fills an important niche within small, rural communities such as those found within Appalachia. Patients in these regions cannot afford expensive testing. Moreover, they often develop strong ties with their physicians, whom they see infrequently due to travel and cost constraints. An obstetrician/gynecologist working in one of these communities can make a big impact on perinatal birth outcomes by including these two inexpensive yet effective smoking cessation techniques in his/her prenatal care for women.

There are alternatives to cotinine testing. Some clinicians suggest measuring tobacco usage using breath analyses of expired carbon monoxide (eCO). These eCO tests have a half-life of 2–8 hr, allowing detection of smoking over a 6–24 hour period. This reduced half-life requires more frequent testing of eCO (i.e., more trips to the clinic) to obtain more representative measurements of tobacco use. In addition, the process of cigarette smoking is complex. Intake of nicotine during smoking depends on many variables (puff volume, depth of inhalation, the extent of dilution with room air, and the rate and intensity of puffing), all of which can be controlled by the individual. While eCO can be less expensive and more rapid than urine drug testing, this testing method has shown poorer performance at measuring tobacco use than cotinine drugs screens.

There are limitations to our study. Our patient population demonstrates a very high level of tobacco abuse (47% by urine cotinine) compared to the national average of approximately 15%. With an overall high rate of smoking among adults in West Virginia, there has not been the social taboo of smoking during pregnancy that has emerged so predominately in other states over recent decades. There are some possible biases in a retrospective design for a study such as selection bias and information bias. In particular, patients who knew they were being tested for tobacco usage would be less likely to underreport since they would know they were being tested. Study staff had to rely on the accuracy of data recorded on the smoking cessation program assessments and patient medical record. Another issue is with the accuracy of cotinine test. The hydration of a patient can affect the cotinine concentration in urine. One study found that pregnancy has a marked inducing effect in cotinine clearance, 140% in
pregnancy compared to postpartum. Also, the possibility of exposure to passive smoking could be raised as a confounder in patients who reported themselves as non-smokers yet were positive for urine cotinine. However, the high urinary level of cotinine (≥500 ng/mL) makes it unlikely that passive smoke inhalation would lead to a false positive test for urine cotinine. In addition, while we were able to find statistically significant results, the sample size was limited to the availability of data as the new cotinine testing at our clinic began in January 2012, thus leaving only fifteen months to include patients as the birth outcome data is not available for several months later due to length of gestation in pregnancy taking several months.

In this study, we did not address the correlation between additional substances used and perinatal outcomes. Detection of illicit drugs among the pregnant population was 25.8% and alcohol use 7.4%. When comparing these values to how many women smoked in our study – around 50%, based on self-reported use and cotinine levels – it begs the question: “did mothers get the word that alcohol is bad for babies but not tobacco or illicit drugs?” This is why our suggestion to combine self-reports and urine cotinine testing for effective smoking cessation during pregnancy may be more beneficial. When you open conversations with women about tobacco use, you can set the stage to ask about additional drug use and counsel about their deleterious effects. In addition, the Ameritox drug screen tests for additional substances along with cotinine. We can detect these compounds in urine and counsel women who may not be as forthcoming about their choices.

Our study also had several strengths. Our data collection tool assessing tobacco usage on all obstetric patients in the clinic had been in place and administered by trained staff since 2006. With clinic data on the smoking rate reported quarterly, study staff are confident that the self-report rate in this study is accurate as this data is similar to the rate reported during the past year. In addition, we obtained self-reported tobacco use and blood draws for cotinine testing during the same prenatal visit. Finally, all lab work was processed in a central core lab.

While only cotinine results were significantly associated with some of the birth outcomes, both cotinine levels and self-reported smoking status were comparable with respect to associations with head circumferences, birth length, birth weight, NAS, and the composite poor outcome. Adverse birth outcomes require enormous medical costs and when only a few cases are prevented, substantial savings can occur. Cotinine testing may play a beneficial role in identifying patients who might be in need for targeted smoking cessation that could not be identified through self-report. Cotinine testing remains particularly applicable in rural, smaller
communities since it is relatively cheap (approximately $10/test), allows early identification of smokers, and targeting of those patients benefitting most from smoking cessation/reduction efforts. Tobacco cessation/reduction is particularly important in rural areas since smaller hospitals are not equipped to care for preterm deliveries <34 weeks or significantly IUGR neonates. Our study population had a high disclosure rate compared to many populations that have been reported in the literature. Studies need to assess the cost-benefit analysis of adding cotinine testing to prenatal care to reduce maternal smoking and ultimately the rate of poor fetal outcome.

The authors report no conflict of interest.
References


Table 1. Maternal Characteristics (n=469)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N(%) or ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>25.68 ±5.7</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>372 (79.3%)</td>
</tr>
<tr>
<td>African-American/Black</td>
<td>76 (16.2%)</td>
</tr>
<tr>
<td>Asian American</td>
<td>9 (1.9%)</td>
</tr>
<tr>
<td>More than 1</td>
<td>11 (2.3%)</td>
</tr>
<tr>
<td>Unreported</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>184 (39.2%)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>285 (60.8%)</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>121 (25.8%)</td>
</tr>
<tr>
<td>No</td>
<td>348 (74.2%)</td>
</tr>
<tr>
<td>Ethanol/Alcohol (n=244)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (7.4%)</td>
</tr>
<tr>
<td>No</td>
<td>226 (92.6%)</td>
</tr>
<tr>
<td>Self-Reported Tobacco Use</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>227 (52.5%)</td>
</tr>
<tr>
<td>No</td>
<td>242 (47.5%)</td>
</tr>
<tr>
<td>Other smokers in household (n=303)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>174 (57.4%)</td>
</tr>
<tr>
<td>No</td>
<td>129 (41.6%)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus (DM)</td>
<td>17 (3.6%)</td>
</tr>
<tr>
<td>Gestational DM</td>
<td>22 (4.7%)</td>
</tr>
<tr>
<td>No</td>
<td>430 (91.7%)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td></td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>28 (6.0%)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>24 (5.1%)</td>
</tr>
<tr>
<td>No</td>
<td>417 (88.9%)</td>
</tr>
<tr>
<td>Qualitative cotinine (n)</td>
<td>p</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>No (drug test assay cutoff was &lt;500 ng/mL)</td>
<td>233 (49.7%)</td>
</tr>
<tr>
<td>Yes (drug test ≥ 500 ng/mL)</td>
<td>236 (50.3%)</td>
</tr>
</tbody>
</table>
| Quantitative cotinine (range: 0-2000 ng/mL) (2000ng/mL was upper limit of test) | 758.8 ±810.5 | <0.001
| Qualitative cotinine < 500 ng/mL                              |       |
| “Not a smoker”                                                | 202 (86.7%) |
| “Smoker”                                                      | 31 (13.1%) |
| Qualitative cotinine ≥ 500 ng/mL                              |       |
| “Not a smoker”                                                | 25 (10.7%) |
| “Smoker”                                                      | 211 (89.4%) |

Data are expressed as mean ± standard deviation unless otherwise indicated.
## Table 3. Significant Birth Outcomes by Cotinine and Self-Reported Tobacco Use (n=469)

<table>
<thead>
<tr>
<th></th>
<th>&lt;500 ng/mL (n=233)</th>
<th>≥500 ng/mL (n=236)</th>
<th>p</th>
<th>Self-Reported Tobacco Use</th>
<th>No (n=227)</th>
<th>Yes (n=242)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head circum. (cm)</td>
<td>33.9 ±2.3</td>
<td>33.15 ±2.5</td>
<td>&lt;0.001</td>
<td></td>
<td>33.8 ±2.3</td>
<td>33.3 ±2.5</td>
<td>0.010</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>49.8 ±3.5</td>
<td>48.4 ±3.3</td>
<td>&lt;0.001</td>
<td></td>
<td>49.7 ±3.5</td>
<td>48.6 ±3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Birth weight (gm)</td>
<td>3266.8 ±635.0</td>
<td>2992.4 ±605.2</td>
<td>&lt;0.001</td>
<td></td>
<td>3238.9 ±663.1</td>
<td>3025.4 ±590.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LBW&lt;2500 (gm)</td>
<td>23 (9.9%)</td>
<td>44 (18.6%)</td>
<td>0.008</td>
<td></td>
<td>25 (11.0%)</td>
<td>42 (14.3%)</td>
<td>0.064*</td>
</tr>
<tr>
<td>PTB&lt;37 weeks</td>
<td>27 (11.6%)</td>
<td>45 (19.1%)</td>
<td>0.029</td>
<td></td>
<td>27 (11.9%)</td>
<td>45 (18.6%)</td>
<td>0.054*</td>
</tr>
<tr>
<td>Poor**</td>
<td>33 (14.2%)</td>
<td>59 (25.0%)</td>
<td>0.004</td>
<td></td>
<td>35 (15.4%)</td>
<td>57 (23.6%)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Data are expressed as mean unless otherwise indicated.
*Not significant
**Poor fetal outcomes are defined as small for gestational age, preterm birth, or low birth weight