Serum Cotinine Concentration and Self-reported Smoking during Pregnancy

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Although during pregnancy there is a better correlation between maternal serum cotinine concentration and adverse outcome than between self-reported smoking and such an outcome, few studies of pregnancy have measured cotinine concentration to determine how much a woman smokes. This study assessed the accuracy of self-reported smoking during pregnancy by performing serum cotinine assays on 448 women registered in the Collaborative Perinatal Project (1959–1966). Based on the assumption that a serum cotinine concentration of >10 ng/ml represented active smoking, 94.9% of women who denied smoking and 87.0% of women who stated that they smoked (kappa = 0.83) reported their status accurately. Among smokers, the correlation coefficient between cotinine concentration and number of cigarettes smoked per day was 0.44. Serum cotinine concentration correlated more strongly than self-reported smoking with infant birth weight (r = 0.246 vs. 0.200). In conclusion, this study showed that pregnant women accurately reported whether they smoked, but cotinine concentration was a better measure than self-report of the actual tobacco dose received. Am J Epidemiol 1998;148:259–62.

cotinine; pregnancy; smoking

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Abbreviation: CI, confidence interval.

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MATeRIALS AND METHODS

The subjects for this study were 452 pregnant women who registered in the Collaborative Perinatal Project (1959–1966). Details of the project have been described previously (5). Serum was obtained from each woman when she registered and at regular intervals thereafter. Since then, the serum has been stored at −20°C. These women gave birth to liveborn infants of ≥28 weeks' gestation and were controls in an ongoing nested case-control study of serum caffeine metabolites and spontaneous abortion. As controls, they had serum drawn on the same day of gestation as a woman who experienced a spontaneous abortion; therefore, both cases and controls registered for prenatal care before 20 weeks of gestation. During every prenatal visit, each woman was asked the number of cigarettes she currently smoked per day; this information was missing for four women. No information was collected on passive exposure to smoke. For our report, information on self-reported smoking was obtained at a woman's first prenatal visit.

The cotinine assays were performed by using Micro-Plate Enzyme Immunoassay kits (STC Diagnostics, Bethlehem, Pennsylvania) and following the instructions in the manufacturer's package insert, with two exceptions. First, the sample volume that was analyzed was increased from 25 to 50 μl. Second, 50 μl of deionized water were added to each well of the
95 percent confidence interval (CI) 0.77-0.88). The smoking on a less-than-daily basis, and all 10 had African-American women. Ten women reported kappa value was 0.80 for white women and 0.90 for ing had concentrations of >10 ng/ml (kappa = 0.83, ml, whereas 87.0 percent of those who reported smok- 94.9 percent had cotinine concentrations of ^10 ng/ TABLE 1. Concordance between smoking as determined by self-report and by serum cotinine concentration among women (n = 448) in the Collaborative Perinatal Project, 1959-1966

<table>
<thead>
<tr>
<th>Self-reported smoking</th>
<th>Serum cotinine concentration* (no.)</th>
<th>≤10 ng/ml</th>
<th>&gt;10 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>243</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25†</td>
<td>167</td>
<td></td>
</tr>
</tbody>
</table>

* Kappa = 0.83.
† Includes 10 women who reported smoking on a less-than-daily basis. If these women are excluded, kappa = 0.87.

Low infant birth weight is the most consistently demonstrated effect of maternal smoking during pregnancy. Of those infants born to the 448 women in this study, serum cotinine concentration explained 6 percent of the variance (based on the \( R^2 \) of a simple linear model) and self-reported number of cigarettes smoked per day explained 4 percent of the variance in birth weight. When the analysis was restricted to those women who reported smoking, the numbers were 5.9 percent and 1.4 percent, respectively.

Table 2 gives the results of analyses in which either self-reported smoking or serum cotinine concentration was considered a confounding factor for the relation between several maternal characteristics and mean infant birth weight. The characteristics selected were commonly accepted as associated with both infant birth weight and cigarette smoking; paraxanthine (the primary metabolite of caffeine) was included because it was the factor of interest in the case-control study. Among all women, the results adjusted for serum cotinine concentration were generally similar to those obtained by adjustment for self-reported number of cigarettes smoked. The differences between cotinine- and report-adjusted results were greater in those analyses restricted to women who smoked.

To evaluate how desiccation of these 30-year-old serum samples affected the results of this study, the concentration of sodium was measured in 359 samples and osmolality was measured in an additional 86 (three women had neither measure). The mean concentration of sodium was 149.2 (standard deviation, 25.5) mEq/liter, and the mean osmolality was 307...
women (2, 9). We found that at comparable levels of nicotine pharmacokinetics might have differed among smoking, African-American women had serum co-
cohaled, or whether the cigarettes were filtered; and cigarettes they actually smoked, how deeply they in-
smoked each day; there might have been differences in
explanations for this finding. Women may not have
been aware of the exact number of cigarettes they
smoked per day. There are several possible
returns smoked per day. There are several possible
in this study. This finding suggests that deterioration of
the specimens was minimal.
In this study, as in previous ones (3), the correlation
between maternal serum cotinine and infant birth weight was stronger than the correlation between ma-
ternal self-reported smoking and infant birth weight.
The Collaborative Perinatal Project and its contempo-
rary, the Child Health and Development Studies, are
still commonly analyzed to investigate risk factors for
a variety of adverse pregnancy outcomes. Is it suffi-
cient to accept self-reports of active maternal smoking,
or is it necessary to employ a biomarker for smoking?
At least in these cohorts from the 1960s, our results
and those of English et al. (4) suggest that if smoking is considered as any or none, then self-reports are
sufficiently accurate, and little would be gained by
biochemical verification. If the dose-response effect
of smoking is the exposure of interest, particularly
among women who smoke, then the more than four-
fold increase in birth weight variance explained by
serum cotinine concentration versus self-report (5.9
vs. 1.4 percent) suggests that consideration be given to
use of cotinine. If the dose response of smoking is of
interest solely as a confounding factor, then the benefit of substituting cotinine concentration for self-report
depends on the strength of the associations between
smoking and pregnancy outcome, smoking and the
risk factor of interest, and self-reported smoking and
cotinine concentration (11, 12). If the population is
restricted to smokers, then measurement of cotinine
concentration may make a meaningful difference in
the adjusted effects of other factors. In a population of
both smokers and nonsmokers, the benefits are more
variable. However, it may be possible to utilize self-
reported smoking and serum cotinine concentration
from a small subsample of the women to derive a
method to adjust the regression coefficients of other

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**TABLE 2. Change in infant birth weight by maternal factors, adjusted for self-reported smoking or serum cotinine concentration, among women (n = 448) in the Collaborative Perinatal Project, 1959–1966**

<table>
<thead>
<tr>
<th>Maternal factor</th>
<th>Change in Infant birth weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All women</td>
</tr>
<tr>
<td>Pre-pregnancy weight (g/kg)</td>
<td>8.1</td>
</tr>
<tr>
<td>Adjusted for self-reported smoking*</td>
<td>7.3</td>
</tr>
<tr>
<td>Adjusted for serum cotinine concentration</td>
<td>7.2</td>
</tr>
<tr>
<td>Years of education (g/year)</td>
<td>33.4</td>
</tr>
<tr>
<td>Adjusted for self-reported smoking*</td>
<td>23.4</td>
</tr>
<tr>
<td>Adjusted for serum cotinine concentration</td>
<td>16.1</td>
</tr>
<tr>
<td>Gestational weight gain (g/kg)</td>
<td>35.3</td>
</tr>
<tr>
<td>Adjusted for self-reported smoking*</td>
<td>38.4</td>
</tr>
<tr>
<td>Adjusted for serum cotinine concentration</td>
<td>34.7</td>
</tr>
<tr>
<td>Serum paraxanthine† (g/ng/ml)</td>
<td>-0.047</td>
</tr>
<tr>
<td>Adjusted for self-reported smoking*</td>
<td>0.014</td>
</tr>
<tr>
<td>Adjusted for serum cotinine concentration</td>
<td>0.017</td>
</tr>
</tbody>
</table>

* Number of cigarettes smoked per day, continuous variable.
† Paraxanthine = primary caffeine metabolite, measured at <140 days of gestation.

(standard deviation, 75) mOsm/kg. There was no sta-
tistically significant correlation between either sodium
concentration or osmolality (r = −0.06 and 0.02,
respectively) and serum cotinine concentration.

**DISCUSSION**

The results of this study are similar to those of
English et al. (4), who also noted that pregnant women
were very honest in reporting whether they smoked. In
the Collaborative Perinatal Project, serum was usually
obtained when a woman first registered, which might
have been several weeks before the first prenatal visit
and interview. Had the serum been collected closer to
the time of the interview, the concordance might have
been even greater than we observed.

In spite of the accuracy of self-reported smoking as
a binary variable, serum cotinine concentration was
only moderately correlated with the number of cigare-
ettes smoked per day. There are several possible
explanations for this finding. Women may not have
been aware of the exact number of cigarettes they
smoked each day; there might have been differences in
the nicotine content of the cigarettes, how much of the
cigarettes they actually smoked, how deeply they in-
haled, or whether the cigarettes were filtered; and
nicotine pharmacokinetics might have differed among
women (2, 9). We found that at comparable levels of
smoking, African-American women had serum co-
tinine concentrations that were 76 ng/ml higher than
those of white women. This is similar to the difference
of 83.3 ng/ml reported among nonpregnant women (7)
but was greater than the 27.4 ng/ml difference among
pregnant women (4). The median concentration of
cotinine per cigarette smoked was substantially higher
among African-American women as well.

The serum samples may have deteriorated during
prolonged storage. While there is little information on
the long-term stability of serum cotinine, the findings
from urinary cotinine samples assayed after being
stored for 11 years at −20°C clearly separated self-
reported smokers from nonsmokers (10). In reporting
on a predominantly white population of pregnant
women, Haddow et al. (6) found a median cotinine
concentration of 9.4 ng/ml per cigarette smoked, al-
most identical to the value of 9.7 that we observed in
this study. This finding suggests that deterioration of
the specimens was minimal.

In this study, as in previous ones (3), the correlation
between maternal serum cotinine and infant birth
weight was stronger than the correlation between ma-
ternal self-reported smoking and infant birth weight.

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exposures for the imperfectly measured confounder of self-reported smoking (13). Such a procedure would spare the expense and biologic resources required to measure cotinine concentration in every subject.

As recently as the 1980s, young adults were found to report their smoking with an accuracy similar to that noted here (7). However, in more recent times, pregnant women often receive vigorous counseling to quit or to reduce their level of smoking, and their incentive to misreport may be greater (14). Therefore, before the results of this study are generalized, they should be replicated in more contemporary cohorts of pregnant women.

ACKNOWLEDGMENTS

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REFERENCES