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

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
To maintain comparability with previous studies (4, 7), we performed analyses using untransformed cotinine. Agreement between amount of smoking as determined by self-report and by serum cotinine concentration was assessed using the kappa statistic; values of ≥0.75 were considered excellent. Ninety-five percent confidence intervals for kappa were calculated using the methods described by Fleiss (8). Correlations between continuous variables were assessed by using the Pearson coefficient and simple linear regression, and adjusted differences were assessed by using multiple linear regression. The Wilcoxon rank-sum test was used to compare medians.

RESULTS

A total of 452 women were selected for this study; 192 (42.4 percent) reported that they smoked and 256 (56.6 percent) reported that they did not. Smoking status was missing for four women. Information on the association between active smoking as determined by self-report and by serum cotinine concentration is presented in table 1. Among women who denied smoking, 94.9 percent had cotinine concentrations of ≤10 ng/ml, whereas 87.0 percent of those who reported smoking had concentrations of >10 ng/ml (kappa = 0.83, 95 percent confidence interval (CI) 0.77–0.88). The kappa value was 0.80 for white women and 0.90 for African-American women. Ten women reported smoking on a less-than-daily basis, and all 10 had cotinine concentrations of ≤10 ng/ml. When these women were excluded, the kappa value increased to 0.87 (95 percent CI 0.82–0.92). Among women who reported that they currently smoked, the correlation between serum cotinine concentration and the number of cigarettes smoked per day was 0.44 (0.44 for white women and 0.66 for African-American women). African-American women who smoked reported smoking an average of 8.3 cigarettes a day versus 6.7 for white women. In spite of this small difference, the mean serum cotinine concentration was more than twice as high among African-American smokers as it was among white smokers (232 vs. 98 ng/ml). After we controlled for age, education, parity, years of smoking, and number of cigarettes smoked per day (4), the mean serum cotinine concentration of African-American women was 76 ng/ml higher than that of white women (95 percent CI -8 to 160). Among white women who smoked, the median cotinine concentration per cigarette smoked was 9.7 ng/ml versus 22.4 among black smokers (p < 0.001).

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 the cigarettes they actually smoked, how deeply they inhaled, or whether the cigarettes were filtered; and how many cigarettes they smoked per day. There might have been differences in the nicotine content of the cigarettes, how much of the cigarette was smoked each day; there might have been awareness of the exact number of cigarettes they smoked. There are several possible explanations for this finding. Women may not have been aware of the exact number of cigarettes they smoked per day. In spite of the accuracy of self-reported smoking as a binary variable, serum cotinine concentration was 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/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.

In this study, as in previous ones (3), the correlation between maternal serum cotinine and infant birth weight was stronger than the correlation between maternal self-reported smoking and infant birth weight. The Collaborative Perinatal Project and its contemporaries, the Child Health and Development Studies, are still commonly analyzed to investigate risk factors for a variety of adverse pregnancy outcomes. Is it sufficient 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 non, 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

(standard deviation, 75) mOsm/kg. There was no statistically 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 cigarettes 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 inhaled, 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 cotinine 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, almost 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 maternal self-reported smoking and infant birth weight. The Collaborative Perinatal Project and its contemporaries, the Child Health and Development Studies, are still commonly analyzed to investigate risk factors for a variety of adverse pregnancy outcomes. Is it sufficient to accept self-reports of active maternal smoking, or is it necessary to employ a biomarker for smoking?
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