

## A B S T R A C T

This study describes the prevalence of smoking among 3,220 pregnant women. Maternal and umbilical cord cotinine levels were compared with the women's self-reported cigarette consumption, infant birth weight and antepartum and perinatal complications. Of the women who reported themselves as being active smokers (23%), 76% had a partner who smoked, and 38% reported exposure to environmental smoke in the workplace. Only 15% of nonsmokers had a partner who smoked, and 13% reported workplace exposure. The mean number of cigarettes/day was 20.5 (95% CI 19.6-21.4). The relative risk of having a small-for-gestational-age infant was significantly higher in smokers for mothers of both preterm (34-36 wks, RR= 3.38, 95% CI 1.25 - 9.16) and term babies ( $\geq 37$ wks, RR= 2.04, 95% CI 1.58 - 2.63). Mean infant birth weight was 207 g lighter in the infants of smokers ( $p < 0.001$ ) and was inversely correlated to maternal serum cotinine level. Birth weight dropped by 0.99 g for every 1 ug/L increase in cotinine ( $r = -0.19$ ,  $p < 0.01$ ).

## A B R É G É

Cette étude décrit la prévalence du tabagisme durant la grossesse, auprès de 3 220 Canadiennes. Les taux sanguins de cotinine de la mère et du cordon ombilical ont été comparés à la consommation de cigarettes déclarées par les participantes, au poids des nourrissons à la naissance et aux complications périnatales et postnatales. Parmi celles qui avouaient fumer activement (23 %), 76 % avaient un conjoint fumeur et 38 % étaient exposées à la fumée dans leur milieu de travail. Seulement 15 % des non fumeuses cohabitaient avec un fumeur, et 13 % rapportèrent être exposées à la fumée dans leur milieu de travail. La consommation moyenne s'élevait à 20,5 cigarettes/jour (95 % IC; 19,6 - 21,4). Le risque relatif de donner naissance à un bébé de petit poids prématuré (34-36 semaines; RR = 3,38; 95 % IC 1,25 - 9,16) ou à terme ( $\geq 37$  semaines; RR = 2,04; 95 % IC 1,58 - 2,63) était significativement plus élevé chez les fumeuses. Le poids moyen des nourrissons à la naissance issus de mères fumeuses était de 207 g inférieur à celui des nourrissons de mères non fumeuses ( $p < 0,001$ ), et était inversement proportionnel aux taux sanguins maternels de cotinine. En fait, le poids des nourrissons à la naissance diminuait de 0,99 g pour chaque augmentation de 1  $\mu\text{g/L}$  de cotinine sanguin chez la mère ( $r = -0,19$ ;  $p < 0,01$ ).

# A Canadian Tertiary Care Centre Study of Maternal and Umbilical Cord Cotinine Levels as Markers of Smoking During Pregnancy: Relationship to Neonatal Effects

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Cigarette smoking during pregnancy continues to be a major health problem in many countries. Despite the results of numerous studies<sup>1-7</sup> demonstrating decreased birth weight, increased incidence of intrauterine growth retardation, placental dysfunction, perinatal morbidity and mortality, and poor childhood physical and neurodevelopment, a large percentage of women of childbearing age continue to smoke.<sup>8-11</sup>

Of the adverse effects associated with smoking during pregnancy, low birth weight remains one of the most important public health issues. Mittendorf et al<sup>12</sup> reported that cigarette smoking causes 34% of all known preventable low birth weights in the United States. Other studies have demonstrated improvements in fetal outcomes after initiation of intervention programs to reduce smoking in pregnant women.<sup>13-15</sup> Reports of the dose-response relationship between smoke exposure in pregnant women and low birth weight have been semiquantitative<sup>16,17</sup> because of complicating factors such as inaccuracy of self-reported cigarette exposure, variations in inhalation technique, variability in nicotine content of individual brands and secondary environmental exposure. Recently, cotinine — a major metabolite of nicotine — has been used as a biochemical marker

to verify patient-reported smoking history and to quantify tobacco smoke intake and environmental exposure.<sup>18-23</sup> We monitored 3,220 births to evaluate the prevalence and impact of smoking on pregnant women. Serum cotinine levels were measured in maternal and umbilical cord samples from active smokers or women regularly exposed to environmental tobacco smoke. Our primary objective was to compare cotinine levels with patient-reported smoking habits and evaluate the relationship to birth weight. Secondary end points included the prevalence of other antepartum or neonatal complications in smokers vs nonsmokers.

## METHODS

All women presenting to the labour and delivery room (LDR) between July 1989 and May 1990 were invited to participate in the study. Complete obstetrical and smoking histories were obtained through a questionnaire administered by a staff member of the LDR who was not involved in the study (resident, intern, medical student, or nurse) to a total of 3,220 subjects. For active smokers, cigarette consumption was quantified as less than 5, 5-9, 10-19, 20-39 or more than 40 cigarettes/day. The study population included patients followed by general practitioners and obstetricians as well as those attending a high risk pregnancy unit. Gestational ages were established from the last menstrual period alone ( $n = 777$ ) or by last menstrual period with ultrasound confirmation prior to 20 weeks' gestation ( $n = 2433$ ).

Maternal blood for cotinine measurement was collected by venipuncture in

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lithium heparin Vacutainers™ at the same time that routine blood work was done, usually at time of presentation to the LDR. For cotinine analyses, umbilical arterial (n=109) and venous (n=751) cord blood was collected in heparinized syringes from the unclamped cord after delivery of the baby but before placental expulsion. The interval between maternal and fetal sampling was recorded. Blood was stored on ice, transferred to the laboratory and centrifuged for 10 minutes at 3,000 xg to separate plasma, which was stored at -70°C until analyzed.

Plasma cotinine concentration was determined using a modified radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA) as previously described.<sup>24</sup> Since smoking is prohibited in the LDR, the time between maternal and umbilical cord sampling represented the woman's abstinence from smoking. The half-life of cotinine clearance from maternal-fetal circulation during smoking abstinence was determined from the slope of Log (Cord [Cotinine]/Maternal [Cotinine]) x 100% vs Time Interval Between Maternal and Fetal Sampling (i.e., length of maternal abstinence).

Clinical and laboratory data were evaluated using EpiInfo Version 5.01 (Centers for Disease Control, Atlanta, GA).

This study was approved by the hospital's Research Ethics Committee.

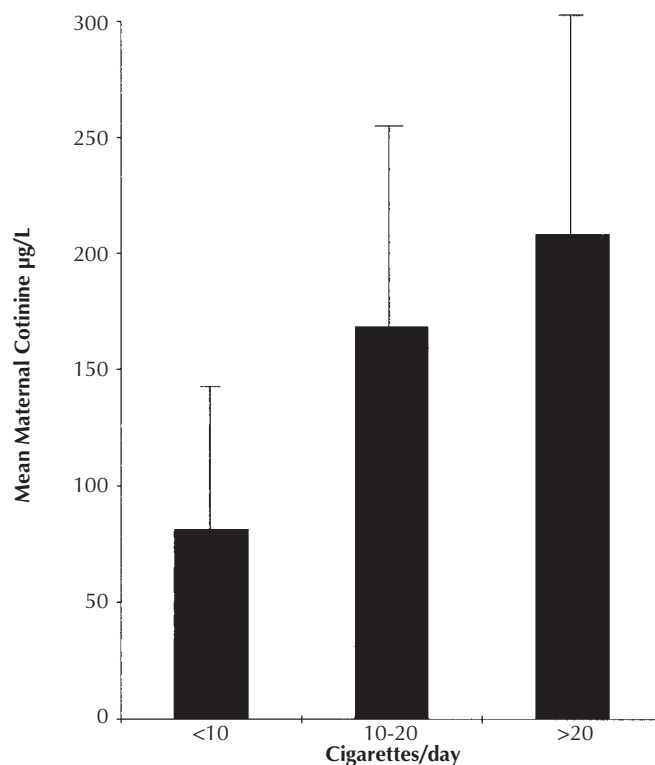
## RESULTS

### Demographics characteristics

Table I lists the characteristics of the study population. Of 3,220 women who participated in the study, 734 (23%) were active smokers. Only 15% of nonsmokers had partners who smoked, whereas 76% of smokers' partners also smoked. Smokers were on average 2.5 years younger than nonsmokers ( $p < 0.0001$ ). The percentage of smokers decreased with age: 17-21 years, 53%; 22-26, 29%; 27-31, 21%; 32-36, 15%; and older than 37, 11%. There was no significant difference between average parity, gestational age or sex of the baby in the smoking and nonsmoking groups.

**TABLE I**  
**Demographic Characteristics of Smoking and Nonsmoking Pregnant Women (n=3220)**

| Characteristic                                 | Nonsmokers             | Smokers                |
|--|------------------------|------------------------|
| Number   | 2486 (77%)             | 734 (23%)              |
| Partner smoker                                 | 360 (15%)              | 76%                    |
| Workplace smoke exposure                       | 316 (13%)              | 38%                    |
| Cigarettes/day                                 |                        |                        |
| <10  |                        | 32%                    |
| 10-20  |                        | 44%                    |
| 21-40  |                        | 23%                    |
| >40  |                        | 1%                     |
| Mean maternal age (95% confidence interval)    | 29.8 years (29.6-30.0) | 27.3 years (26.9-27.6) |
| Parity   |                        |                        |
| 1  | 35%                    | 32%                    |
| 2  | 34%                    | 32%                    |
| ≥3   | 31%                    | 36%                    |
| Mean gestational age (95% confidence interval) | 39.1 weeks (34.9-43.5) | 38.9 weeks (33.9-43.9) |

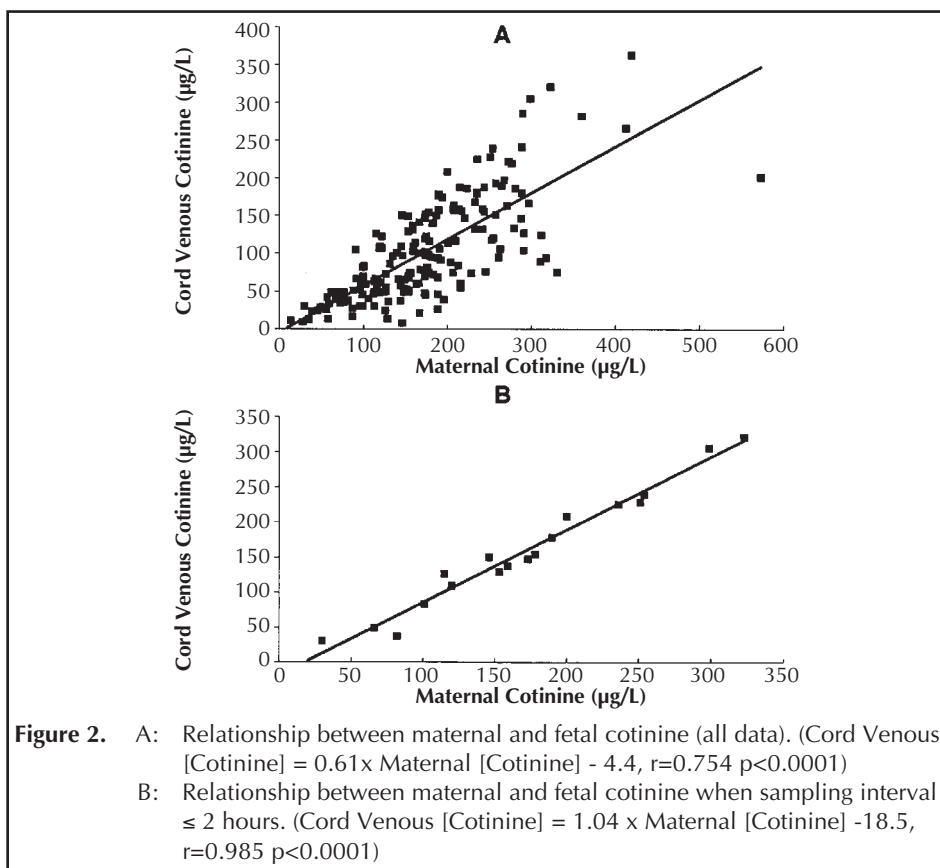


**Figure 1.** Relationship of maternal cotinine to patient-reported smoking history. Mean values and 1 SD error bars are shown.

### Cotinine levels and distribution

Figure 1 shows the relationship between cotinine level in the patient and reported number of cigarettes smoked per day. The mean number of cigarettes smoked per day was 20.5 (95% CI 19.62-21.4). A total of 679 samples were analyzed from women

who reported themselves as active smokers; the mean maternal cotinine level in this group was 152 µg/L (range 2-500 µg/L). Cotinine levels were undetectable in 89 of 107 specimens from women who were self-reported nonsmokers but whose partners smoked. Thirteen specimens had levels of



from the slope of the graph (Figure 3) of Log (Cord/Maternal [Cotinine] x 100) vs Time Interval Between Maternal and Fetal Sampling:

$$t_{1/2} = 0.693 / (-\text{slope} \times 2.203) = 16.3 \text{ hours}$$

**Antepartum and neonatal complications**

Table II summarizes the incidence of selected maternal and neonatal complications in nonsmokers and smokers. There were no differences in the incidence of placental dysfunction, preterm delivery or maternal hypertension. No statistically significant differences were seen in two indicators of fetal hypoxia: 1 minute Apgar score and umbilical venous pO<sub>2</sub>. A small but statistically significant difference was seen in umbilical arterial pO<sub>2</sub>.

**Effect on birth weight**

The incidence of small-for-gestational-age (SGA) babies in smokers vs nonsmokers is summarized in Figure 4. SGA was defined as birth weight less than the 10th percentile for each gestational age according to the 1986 standards of Health & Welfare Canada.<sup>25</sup> Overall, infants of smokers were on average 207 g lighter (p<0.001) than those of nonsmokers.

To examine the relationship between smoking intensity and birth weight, the data were sorted by cotinine level into groups of light, moderate and heavy smokers. Mean birth weights for each of the cotinine tertiles showed that babies born to nonsmoking mothers weighed significantly more than those born to smokers in a cotinine-dose-dependent manner (Table III). It was impossible to examine separately these effects in active smokers vs women regularly exposed to environmental or passive smoke since only 15% of nonsmokers reported environmental exposure, and cotinine levels were undetectable in the majority of their samples.

**DISCUSSION**

The incidence of smoking during pregnancy is known to vary with race, education, socioeconomic status and geographic location.<sup>2,10</sup> Our study population was predominantly middle-class Caucasian representing a white collar population base of

|  | Nonsmokers  | Smokers     | t-test p-value |
|--|-------------|-------------|----------------|
| Abruptio placenta                        | 1.4%        | 2.0%        | ns             |
| Placenta previa                          | 0.8%        | 0.14%       | ns             |
| Preterm delivery                         | 8.5%        | 9.5%        | ns             |
| Multiple variable decelerations          | 8.0%        | 10.9%       | ns             |
| Pregnancy induced hypertension           | 6.8%        | 5.9%        | ns             |
| Median 1 min Apgar                       | 8.0         | 8.0         | ns             |
| Median 5 min Apgar                       | 9.0         | 9.0         | ns             |
| Mean umbilical arterial pH               | 7.3 ± 0.1   | 7.3 ± 0.07  | ns             |
| Mean umbilical arterial pO <sub>2</sub>  | 20.7 ± 9.9  | 19.5 ± 8.2  | 0.003          |
| Mean umbilical arterial pCO <sub>2</sub> | 48.2 ± 12.4 | 47.9 ± 10.3 | ns             |
| Mean umbilical venous pH                 | 7.3 ± 0.1   | 7.3 ± 0.06  | ns             |
| Mean umbilical venous pO <sub>2</sub>    | 30.2 ± 7.7  | 29.6 ± 7.9  | 0.092          |
| Mean umbilical venous pCO <sub>2</sub>   | 40.2 ± 7.3  | 40.3 ± 6.5  | ns             |

<10 ug/L, and one specimen had a level (181 ug/L) consistent with that of an active smoker.

Maternal-fetal distribution of cotinine was evaluated by comparing paired maternal and umbilical cord venous cotinine samples (Figure 2A). A poor correlation was seen in these data because the time interval between maternal and umbilical cord sampling was extremely variable, depending on the stage of labour at the time of presentation to the LDR and length of labour. When the sampling interval was

less than 2 hours (Figure 2B) there was a direct, linear relationship between maternal and umbilical cord cotinine (Cord Venous [Cotinine] = 1.04 x Maternal [Cotinine] - 18.5 r=0.985, p<0.0001).

Comparison of arterial and venous umbilical cord concentrations revealed no significant fetal metabolism or sequestration of cotinine (data not shown). (Arterial [Cotinine] = 1.00 x Venous [Cotinine] - 1.3; n=47 r=0.9799, p<0.0001.)

Maternal-fetal cotinine clearance with abstinence from smoking was determined

approximately one million. Almost one-quarter of the women were active smokers. Less than 15% of nonsmokers had a partner who smoked, whereas 76% of smokers reported that their partner was also an active smoker. Only 13% of nonsmokers and 38% of active smokers reported exposure to environmental smoke in their workplace.

Wen et al<sup>2</sup> in a study of women in Birmingham, Alabama, found that the proportion of smokers increased with maternal age. Similarly, in a 1989 survey by Health & Welfare Canada<sup>11</sup> it was found that only 24% of 15-19 year old women were current smokers in contrast to 38% of 20-24 year olds and 36% of 25-34 year olds. In our study, smokers were, on average, 2.5 years younger than nonsmokers. Studies are now under way to determine whether the prevalence of smoking in pregnant women has varied with recent changes to Canadian laws governing tobacco advertising and decreased taxation of tobacco products.

The primary end point of this study was to examine the effects of maternal smoking on birth weight. We also compared the prevalence of numerous other maternal and neonatal clinical complications in smokers and nonsmokers. Small differences were observed for two of the three indicators of fetal hypoxia: median one minute Apgar scores were identical in the two groups, but there were lower venous and arterial pO<sub>2</sub> levels in smokers. The prevalence of other complications (Table II) historically associated with maternal smoking was not greater in this study; however, these complications are uncommon in our population as a whole and so we would have required a substantially larger sample to detect a difference between the two groups. Overall, mean birth weights were 207 g (p<0.001) lighter in the babies of smokers. Figure 4 demonstrates that this effect was also reflected in the SGA infants. The relative risk of SGA was high in both preterm (RR=3.38, 95% CI 1.25-9.16, p= 0.0197) and term (RR=2.04, 95% CI 1.58-2.63, p<0.0001) infants.

The specific physiological and biochemical effects of maternal cigarette smoking in pregnancy have not been completely eluci-

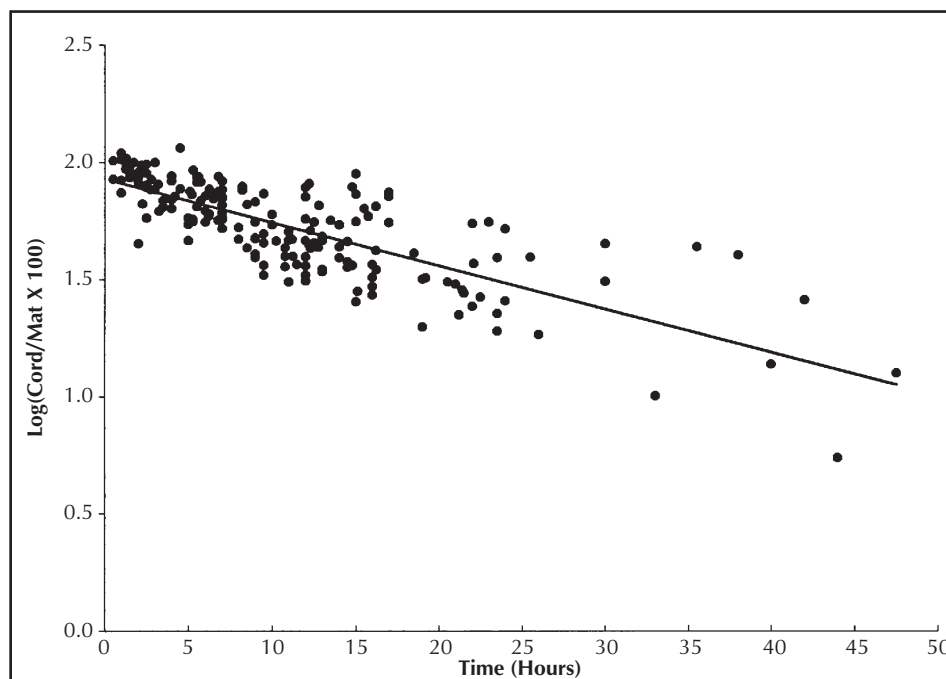


Figure 3. Maternal-fetal cotinine clearance during maternal abstinence from smoking.

TABLE III  
Relationship of Smoking Habit to Birth Weight and Gestational Age

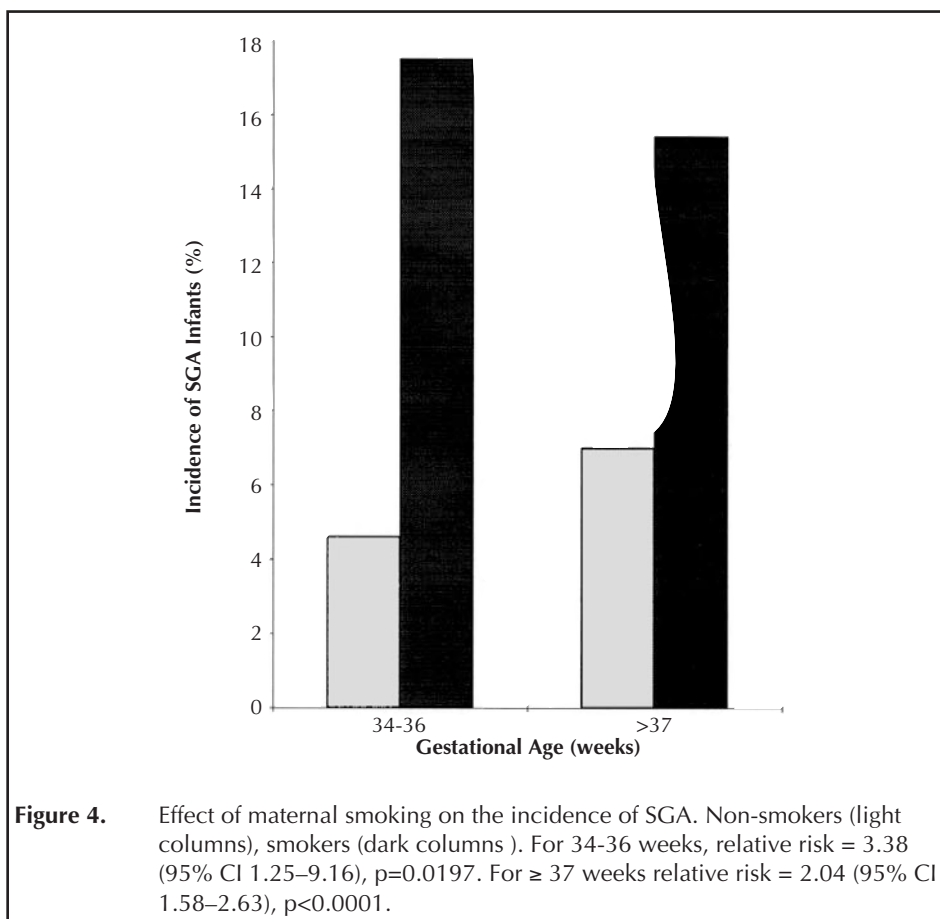
| Smoking Habit (cotinine mg/L)             | Mean Birth Weight (g)<br>(95% confidence interval) | Mean Gestational Age (wks)<br>(95% confidence interval) |
|---|--|---|
| Nonsmokers + no passive exposure (n=1884) | 3407<br>(3380-3434)                                | 39.1<br>(39.0-39.2)                                     |
| Nonsmokers + passive exposure (n=524)     | 3467<br>(3386-3477)                                | 39.4<br>(39.3-39.6)                                     |
| Light (10-113 mg/L) (n=163)               | 3403<br>(3296-3510)                                | 39.4<br>(39.1-39.8)                                     |
| Moderate (114-193 mg/L) (n=146)           | 3202*<br>(3083-3321)                               | 39.3<br>(38.9-39.6)                                     |
| Heavy (193-419 mg/L) (n=122)              | 3161*<br>(3045-3275)                               | 39.1<br>(38.8-39.4)                                     |

\* p<0.0005 compared with nonsmokers

dated. Correlations between patient-reported cigarette consumption and maternal and neonatal complications have been weak and subject to criticism because of the high variability associated with self-reported data. Many epidemiological studies<sup>18-23</sup> have used cotinine, a major metabolite of nicotine, as a biochemical marker of exposure to tobacco products. In this study we found a good correlation between patient reported smoking history and cotinine concentrations (Figure 1). Patients' reporting of cigarette consumption as discrete fractions of packs per day results in noncontinuous data which, along with

variations in both the nicotine content of various brands and the inhalation technique, contribute to the overlap between the groups shown in Figure 1. A relatively poor correlation was observed initially between maternal and umbilical cord venous cotinine levels (Figure 2A). However, when the time between maternal and umbilical cord sampling was two hours or less, the correlation improved to near unity. This suggests that cotinine equilibrates across the placenta. For samples separated by more than two hours, the umbilical cord concentration was always less than that of the mother. Since expect-





tant mothers were not allowed to smoke in the hospital it was presumed that this difference represented active clearance of cotinine from the fetal circulation during maternal abstinence. This allowed us to calculate the half-life of cotinine in maternal-fetal circulation as 16.3 hours, a value similar to previously reported adult values.<sup>26</sup>

The linear relationship between maternal and fetal cotinine levels that we observed is similar to that previously reported by Luck et al,<sup>27</sup> but they found high levels of nicotine in umbilical vein serum and placental tissue compared with maternal serum. The half-life of nicotine in blood is much shorter than that of cotinine (approximately 2 hrs vs approximately 16 hrs), and the more hydrophilic cotinine has a smaller volume of distribution than nicotine.<sup>26</sup> This may explain the higher levels of nicotine that Luck et al<sup>27</sup> observed in placental tissue and fetal circulation. To investigate whether sequestration and/or metabolism of cotinine occurs in the fetus we compared cotinine concentrations in

umbilical venous and arterial plasma. The excellent correlation between paired samples (data not shown) suggests that despite the findings of Luck et al<sup>27</sup> the fetus does not appear to sequester cotinine. In one of the few reported studies of simultaneous maternal and fetal sampling Donnenfeld et al<sup>28</sup> reported fetal cotinine concentrations to be, on average, 90% of maternal values.

Several groups have investigated the relationship between maternal and fetal cotinine levels and birth weight.<sup>28-33</sup> Haddow et al<sup>29,32</sup> studied birth weights from pregnant women in Maine who were exposed to actively inhaled or environmental smoke. The infants of women who smoked 25 cigarettes or more daily were 289 g lighter than those of nonsmokers, and the women who had the highest serum cotinine levels ( $>284$  ug/L) delivered infants who were 442 g lighter. In their passive-exposed group the mean birth weight was 107 g lighter than that in the unexposed group with a linear relationship of -28g per ug/L cotinine. Eskenazi,<sup>30</sup> in a study of Californian women exposed to passive cig-

arette smoke, found birth weight decreased 1 g for every 1 ug/L of cotinine. Other European studies have reported that 1 ug/L of cotinine in maternal serum decreases birth weight by 1.29 g in active smokers in Finland,<sup>31</sup> and passive smoke exposure in Spain<sup>33</sup> resulted in an 87.3 g decrease in birth weight when the maternal serum cotinine level was  $>1.7$  ug/L. Univariate analysis of the relationship between maternal serum cotinine levels and infant birth weight in that study revealed a statistically significant correlation ( $r=-0.19$ , 95% CI -0.28 to -0.10,  $p<0.01$ ) similar to that reported by Haddow et al.<sup>32</sup> The mean maternal cotinine level in our group was 152 ug/L with a 0.99 g (95% CI -0.51 to -1.47) decrease in birth weight for each 1 ug/L increase in maternal cotinine. These data are remarkably similar to those published by US and European groups,<sup>28-33</sup> given that some studies used maternal samples collected during the second trimester, cotinine methodology is not standardized, cigarette nicotine content varies from one country to the next, and some studies were retrospective, one using samples that had been stored up to 25 years.<sup>30</sup>

Plasma cotinine levels were undetectable in the majority of samples tested from our nonsmoking patients who reported passive exposure. This was likely a result of a combination of factors, including choice of specimen (urine is the preferred specimen for detecting passive exposure); time interval from most recent exposure (many of these women had been in active labour before presenting to the LDR, thus it is unlikely they had had significant recent passive exposure); and insufficient low end sensitivity of the assay (the commercial form of the assay is standardized for measurement of urine cotinine levels that are typically 10 to 1000 times that of serum; we modified this assay for measurement of cotinine in serum, but it was unable to detect very low serum cotinine levels associated with passive exposure). It is worth noting that although we did not control for factors such as alcohol or coffee consumption, Eskenazi et al<sup>30</sup> have previously reported that these factors did not improve the relationship of birth weight to maternal cotinine levels. It is possible that, like ciga-

rette smoking, patient-reported consumption of alcohol and coffee may not be reliable.

The results of this study indicate that smoking in pregnancy remains a major health care problem in Canada, contributing to a high risk of SGA and low birth weights. The effect of maternal smoking does appear to have a dose-response relationship to maternal cotinine levels. Although smoking cessation is the optimum goal, women who continue to smoke during pregnancy should be encouraged to consider whatever actions are available to them to decrease their nicotine exposure. Simple options include using low nicotine brands, minimizing inhalation, and decreasing the number of cigarettes smoked.

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