

Expired air carbon monoxide concentration in mothers and their spouses above 5 ppm is associated with decreased fetal growth

Conchita Gomez, Midwife,^{a,b} Ivan Berlin, M.D., Ph.D.,^{c,*}
Pierre Marquis, M.D.,^a and Michel Delcroix, M.D.^b

^aCentre Hospitalier d' Arras, Maternité Georges Pernin, Arras, France

^bAssociation Périnatale Prévention Recherche Information, Bailleul, France

^cService de Pharmacologie, Groupe Hospitalier Universitaire Pitié-Salpêtrière, Paris, France

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Abstract

Background. Smoking during pregnancy is associated with reduced birthweight; this relation can be reversed by smoking cessation. Some but not all previous studies have shown that smoking reduction (measured as cigarettes/day or urinary cotinine) may also improve birthweight. The relationship between maternal and spouses' expired air carbon monoxide (CO) concentrations (EACO) on fetal growth has not yet been evaluated.

Methods. Eight hundred fifty-six smoking and nonsmoking pregnant women were followed during their pregnancy. Their EACO was determined in the first trimester and during delivery. The spouses' EACO were also measured at delivery. The main outcome measure was the infants' birthweight. Secondary measures included head circumference, Apgar score, and heart rate at delivery. Cord blood fetal carboxyhemoglobin (FCOHb) served as internal control.

Results. Birthweight dose-dependently and significantly decreased with increasing level of maternal (0–5: 3406 ± 32 ; 6–10: 3048 ± 57 ; 11–20: 2858 ± 54 ; >20 ppm: 2739 ± 34 g, $P < 0.0001$) or spouses' EACO (0–5: 3546 ± 25 ; 6–10: 3484 ± 51 ; 11–20: 3309 ± 47 ; >20 ppm: 3190 ± 57 g, $P < 0.0001$). Even the birthweight of newborns whose mother had EACO between 6 and 10 ppm was significantly lower than the birthweight of newborns whose mother had an EACO between 0 and 5 ppm. Spouses' EACO of delivering women with EACO of 0–5 ppm showed similar effect. Head circumference, Apgar score, and normal term gestational age decreased also significantly with increasing maternal or spouses' EACO.

Conclusions. Both maternal and spouses' EACO measured during delivery, a proxy of EACO during pregnancy, were dose-dependently and inversely associated with fetal growth. Even low maternal (6 to 10 ppm) or spouses' (11 to 20 ppm) EACO may be associated with significantly lower birthweight.

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Introduction

Tobacco smoking of pregnant women has increased in France during the last 20 years: 14.8% of pregnant women smoked during the third trimester in 1981 [1]; third trimester smoking reached 25.1% in 1995, and it seems to be stable since that time [2]. This prevalence is similar to that reported for the United States [3]. Cigarette smoking during pregnan-

cy adversely affects perinatal morbidity and mortality [4], and it is associated with reduced birthweight [5]. Even light smoking (<5 cigarettes daily) is associated with elevated rates of low birthweight [6]. Maternal smoking may also predict different types of childhood morbidity [3,7–9] and is a risk factor for tobacco dependence in adulthood [10].

Cigarette smoke contains several thousands of chemicals including carbon monoxide (CO) whose amount varies from 10 to 23 mg per cigarette [4]. There is strong evidence that smoking cessation during pregnancy improves neonatal outcome in particular birthweight [11,12] and that non-pharmacological interventions leading to reduction of smoking in pregnant women yield in less birthweight reduction

* Corresponding author. Service de Pharmacologie, Groupe Hospitalier Universitaire Pitié-Salpêtrière, 47, Bd de l'Hôpital, 75013 Paris, Cedex 13, France. Fax: +33-1-42-16-16-88.

E-mail address: ivan.berlin@psl.ap-hop-paris.fr (I. Berlin).

[13]. However, smoking reductions during pregnancy do not seem to reduce significantly loss in birthweight of term infants in all studies [11,14].

Most of the previous studies used self-reported cigarette-per-day consumption to assess the impact of maternal smoking on birthweight; however, use of biochemical markers, for example, cotinine, may give more consistent results [11,14–16].

Expired air CO concentration (EACO) can easily and noninvasively be determined, it does not need a laboratory background, it is used in everyday clinical practice to help smokers quit, and it is a proposed method, along with determination of urinary cotinine concentration to assess lack of smoking in pregnant women [17]. Because CO has demonstrated fetal toxicity and expired air CO takes into account not only active but also passive smoking, expired air CO measurements in pregnant women may offer an adequate approach to estimate in utero exposition to CO and may be associated with unfavorable characteristics of fetal growth.

Therefore, the aim of this study was to assess whether maternal or spouses' expired air CO concentration is associated with birth characteristics. Fetal carboxyhemoglobin (FCOHB) determined in cord blood was used as an internal control.

Methods

This was a monocenter study, realized between May 15, 2001, and September 30, 2003, in an obstetric hospital in Arras, Region Nord-Pas-de-Calais, France. Eight hundred fifty-six consecutive smoking and nonsmoking pregnant women were included. They were included if they had a singleton pregnancy without complication with spontaneous labor by vaginal delivery or programmed cesarean section. Pregnancy should be at normal term (37 to 41 weeks gestation). Women were not included if they had twin pregnancy, reported alcohol abuse or dependence, drug addiction; if they had any chronic medical disease condition, maternal respiratory insufficiency, or any other acute illness at the time of delivery; if there was a suspicion of fetal malformation; if the cardiotocographic recording was less than 1 h; and if no maternal expired air CO was available at delivery or if the amount of cord blood samples was insufficient for fetal carboxyhemoglobin determinations.

All smoking women received a standard brief counseling to help them quit at each prenatal visit. The study protocol was approved by the ethics committee of the Centre Hospitalier of Arras, France. All women and their spouses signed a written informed consent.

For pregnant women, expired air CO measures were taken during the first trimester visit and in the delivery room just before delivery. Spouses' expired air CO was also measured at the time of delivery. The same regularly

calibrated CO tester was used for each measurement (Micro CO Tester, Micro Medical Ltd., Rochester, Kent, UK). Repeated standard calibration showed less than 2% variation during the study. The expired air CO measurement was realized according to detailed written guidelines, and persons performing the measure were trained beforehand. Most of the measures were taken by the first author (CG). When the first author was off-duty, only two other persons were authorized to measure expired air CO.

During delivery, cord blood samples were drawn into a preheparinized blood gas syringe from the umbilical vein (3.5 mL). Blood samples were kept on ice for less than 1 h before transportation at 4°C to the biochemistry laboratory. Fetal carboxyhemoglobin (% of total hemoglobin) was determined by a standard spectrophotometric method distinguishing well carboxyhemoglobin from oxyhemoglobin (Rapidlab 800 series, Module CO-OX 835, Bayer Diagnostics, UK). The interassay coefficients of variation was 12% at a mean of 1% of fetal carboxyhemoglobin.

Fetal heart rate was recorded by a Hewlett-Packard Cardiotocograph (Kent, UK). The normality of fetal heart rate was defined according to criteria of the French National Agency for Accreditation and Evaluations for Health [18]. Briefly, the fetal heart rates were categorized as normal (scores 8 to 10), suspicion of abnormal (scores 6 to 7), and overtly abnormal (≤ 6) according to the score of Fisher and Krebs [18]. The score was calculated after a 30-min recording of fetal heart rate. For data analysis, "suspicion of abnormal" and "abnormal" categories were collapsed into the category "not normal."

Statistical analysis

Variables according to maternal and spouses' expired air CO concentrations were compared by General Linear MANOVA adjusted for maternal age, number of previous pregnancies, and the newborns' sex. Post hoc pairwise comparisons were done by Bonferroni method. Wilcoxon signed rank test was used for dependent sample comparisons. Correlations were tested by Pearson least squares method. Data were analyzed with the statistical package SPSS Version 10.0 (Chicago, IL, USA) and presented as mean (SD) if otherwise not indicated. A *P* value of 0.05 or less was considered significant.

Results

The mean (SD) age of the women was 28 (4.6) years (range: 13 to 42), the mean gestational age was 38.9 (1.2) months (range: 37 to 41), and the mean birthweight was 3198 (525) g (range: 1800 to 4590). This was the first birth in 374 (43.6%), second in 326 (38.1%), and third in 116 (13.6%) cases. Eighteen percent had programmed cesarean section. Ninety-five percent of the women were Caucasian, 1% were of Asian origin, and 4% of African origin. Thirty-

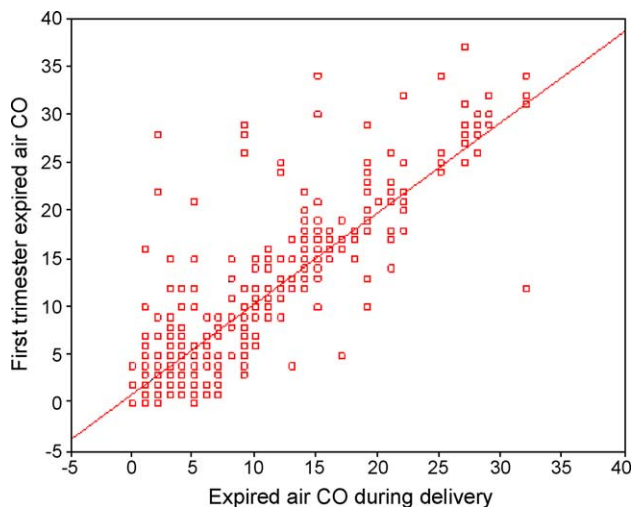


Fig. 1. Relationship between expired air carbon monoxide (CO, ppm) measured during the first trimester of pregnancy and during delivery.

nine percent were married, 38% were living together as husband and wife but not married, and 23% were single. Thirty-six percent had only elementary school education, 48% had high school education, and 16% had college level education. Seventy-five percent were employed, 21% were unemployed, and 4% were students. The mean expired air CO concentration of the pregnant women in the first trimester was 8 (7.5) ppm (range: 0 to 37) and during delivery was 7.4 (6.7) ppm (range: 0 to 32), an average decrease of 0.57 (3.9) ppm ($P < 0.001$). First trimester expired air CO highly correlated with expired air CO during delivery ($R = 0.86$, $CO_{\text{first trimester}} = 1.09 + 0.79 CO_{\text{delivery}}$, $P < 0.0001$) (Fig. 1).

The women smoked a mean of 5.5 (8.3) cigarettes per day (range: 0 to 34) during the first trimester and 4.3 (7) cigarettes per day (range: 0 to 30) during the 7 days before delivery, a mean decrease of 1.1 (4.4) cigarettes per day ($P < 0.001$). The spouses' expired air CO concentration

at delivery was 14.5 (13.3) ppm (range: 0 to 68), and they smoked 10.7 (11.3) cigarettes per day (range: 0 to 50).

Five hundred seven women had expired air CO less than 5 ppm during the first trimester. By the time of delivery, 466 had expired air CO less than 5 ppm. Forty-one women (8.1%) became passively or actively exposed to smoking (expired air CO 0 to 5 ppm in the first trimester and >5 ppm at delivery). Three hundred forty-eight women had expired air CO higher than 5 ppm during the first trimester, from those only 50 (14.4%) became not exposed to smoking (expired air CO of ≤ 5 ppm at delivery).

Table 1 shows delivery characteristics according to the expired air CO measured during delivery. Birthweight decreased in a dose-dependent manner according to increasing maternal expired air CO concentration measured at delivery. Compared to newborns of mothers with expired air CO between 0 and 5 ppm, the birthweight of newborns of mothers with expired air CO between 6 and 10 ppm was significantly lower [mean difference: 450 (43) g]. The mean loss of birthweight was 708 (38) g for those newborns whose mother had expired air CO between 11 and 20 ppm and 754 (59) g for those whose mother had expired air CO higher than 20 ppm at delivery.

Head circumference, Apgar score at 5 min, and gestational age were all significantly lower when maternal expired air CO at delivery was more than 5 ppm compared to maternal expired air CO between 0 and 5 ppm. The mean loss of Apgar score was 0.27 (0.06), 0.33 (0.05), and 0.33 (0.08) with maternal expired air CO of 6 to 10, 11 to 20, and >20 ppm, respectively.

Cord blood fetal carboxyhemoglobin increased dose-dependently with maternal expired air CO. Fetal heart rate during delivery was normal in 84% of cases when maternal expired air CO at delivery was 0 to 5 ppm. Only around half of the newborns from mothers with expired air CO of 6 to 10 had normal fetal heart rate, and only one third of the newborns from mothers with expired air CO between 11 and 20 ppm and >20 ppm had normal heart rate.

Table 1

Newborns' characteristics according to the mothers' expired air carbon monoxide concentration measured during delivery

Expired air carbon monoxide (ppm)	0 to 5, $N = 517$	6 to 10, $N = 113$	11 to 20, $N = 169$	>20 , $N = 57$	P value
Birthweight (g) ^{a,*}	3448 \pm 18	2997 \pm 39	2739 \pm 32	2693 \pm 56	<0.0001
Head circumference (cm) ^{b,*}	35.1 \pm 0.04	34.7 \pm 0.08	34.9 \pm 0.07	35.5 \pm 0.11	<0.0001
Apgar score ^{c,*}	9.7 \pm 0.02	9.5 \pm 0.05	9.4 \pm 0.04	9.4 \pm 0.08	<0.0001
Gestational age (weeks) ^{d,*}	39.1 \pm 0.09	38.6 \pm 0.15	38.5 \pm 0.15	39.8 \pm 0.36	<0.0001
Cord blood fetal carboxyhemoglobin (%) ^{e,*}	1.46 \pm 0.07	2.38 \pm 0.13	3.4 \pm 0.13	5.66 \pm 0.31	<0.0001
Fetal heart rate during delivery [number with normal heart rate (%)] ^{**}	434 (83.9)	65 (57.5)	59 (34.9)	21 (36.8)	<0.0001

Pairwise comparisons (Bonferroni method), $P < 0.05$.

^a 0 to 5 ppm \neq 6 to 10 ppm, 11 to 20 ppm and >20 ppm; 6 to 10 ppm \neq 11 to 20 ppm and >20 ppm.

^b 0 to 5 ppm \neq 6 to 10 ppm and >20 ppm; 6 to 10 ppm \neq 11 to 20 ppm and >20 ppm; 11 to 20 ppm \neq >20 ppm.

^c 0 to 5 ppm \neq 6 to 10 ppm, 11 to 20 ppm and >20 ppm.

^d 0 to 5 ppm \neq 6 to 10 ppm, 11 to 20 ppm and >20 ppm; 6 to 10 ppm \neq 11 to 20 ppm.

^e 0 to 5 ppm \neq 6 to 10 ppm, 11 to 20 ppm and >20 ppm; 6 to 10 ppm \neq 11 to 20 ppm and >20 ppm.

*Data are means (\pm standard errors) adjusted for maternal age, number of previous pregnancies, and newborn's sex from MANOVA [Wilks lambda = 0.348, $F(15,2333) = 72.35$, $P < 0.0001$].

** Chi-square test.

Expired air CO during delivery inversely correlated with birthweight ($r = -0.59$, $P < 0.0001$). The correlation was the best when the logarithm of CO was plotted against birthweight. Multiple stepwise linear regression showed the variables included (expired air CO at delivery, gestational age, number of previous pregnancies, sex of infants, maternal age), birthweight was associated only with expired air CO at delivery and gestational age [$R = 0.63$, $F(2, 848) = 279$, $P < 0.0001$] and that expired air CO explained alone 34% of the variance in birthweight. The gestational age-adjusted birthweight, thus, can be predicted according to: birthweight = $3762 - 794 (\log \text{CO})$ [$R = 0.589$, $F(1, 848) = 450$, $P < 0.0001$].

The effect of 502 spouses' expired air CO of the 507 delivering women with expired air CO between 0 and 5 ppm could be analyzed (Table 2). The spouses' expired air CO was significantly and dose-dependently associated with loss in birthweight [mean difference: -61 (57), -236 (53), and -355 (62) g with spouses' CO of 6 to 10, 11 to 20, and >20 ppm, respectively], head circumference, Apgar score, and increased cord blood fetal carboxyhemoglobin. Increasing expired air CO in spouses was associated with decreasing number of newborns with normal fetal heart rate.

Discussion

This study shows that expired air CO concentration at delivery is inversely associated with birthweight, head circumference, Apgar score, and fetal heart rate. Even low concentrations of maternal expired air CO (6 to 10 ppm), usually considered as incompatible with active smoking, were associated with significantly lower birthweight. Expired air CO concentrations of 6 to 10 ppm were associated with an average adjusted weight loss of 450 g, a 13% loss. Higher expired air CO concentrations yielded weight losses of around 700 g probably tending toward a plateau: infants

of mothers with expired air CO of 11 to 20 ppm lost around 20% and those whose mother had expired air CO higher than 20 ppm lost 22% of weight compared to infants of mothers having expired air CO between 0 and 5 ppm.

Moreover, spouses' expired air CO was also significantly associated with unfavorable birth characteristics in infants of mothers considered as nonexposed to smoking (expired air CO: 0 to 5 ppm). For example, the mean adjusted loss in birthweight was 62, 236, and 355 g with spouses' expired air CO of 6 to 10, 11 to 20, and >20 ppm, respectively, corresponding to weight losses of 2.8%, 6.6%, and 10%, respectively.

To our knowledge, only one previous study assessed the relationship of expired air CO and birthweight. In that study, expired air CO was measured at the first prenatal visit and at the 36th week visit ($N = 350$) [19]. Expired air CO at 36 weeks and birthweight were negatively correlated ($r = -0.32$) (present study: $r = -0.59$). In the Secker-Walker et al. [19] study, no difference in birthweight was found between 36th gestational week's expired air CO of <5 ppm and 5 to 9 ppm contrarily to the present study. The significant difference in birthweight, Apgar score, head circumference, and gestational age between infants from mothers with expired air CO of 0 to 5 and 6 to 10 demonstrated by the present study is of major importance because it suggests that smoking reduction proposed in several studies and in clinical practice is insufficient to completely prevent smoking-induced loss in fetal growth.

The present study shows also that not only the mother's expired air CO is associated with decrease in birthweight, Apgar score, head circumference, and gestational age, but also the expired air CO of spouses, and even low exhaled CO concentration may be associated with detrimental effects in the newborns.

Cotinine-verified smoke exposure of pregnant women is estimated to be of 24%; among those, 38% can be

Table 2

Newborns' characteristics according to the expired air carbon monoxide concentration of spouses of delivering women whose expired air carbon monoxide was between 0 and 5 ppm

Expired air carbon monoxide (ppm) of spouses	0 to 5, $N = 298$	6 to 10, $N = 68$	11 to 20, $N = 81$	>20 , $N = 55$	P value
Birthweight (g) ^{a,*}	3546 ± 25	3484 ± 51	3309 ± 47	3190 ± 57	<0.0001
Apgar score ^{*,b}	9.8 ± 0.03	9.6 ± 0.06	9.8 ± 0.05	9.5 ± 0.07	<0.001
Head circumference (cm) ^{*,c}	35.3 ± 0.05	35.1 ± 0.2	34.5 ± 0.1	35 ± 0.12	<0.0001
Gestational age (weeks) ^{*,d}	39 ± 0.07	39.5 ± 0.14	38.8 ± 0.13	39.1 ± 0.16	<0.001
Cord blood fetal carboxyhemoglobin (%) ^{*,e}	0.99 ± 0.05	1.2 ± 0.1	1.49 ± 0.09	2.64 ± 0.11	<0.0001
Fetal heart rate during delivery [number with normal heart rate (%)] ^{**}	282 (94.6)	55 (80.9)	60 (74.1)	27 (49.1)	<0.0001

Pairwise comparisons (Bonferroni method), $P < 0.05$.

^a 0 to 5 ppm \neq 11 to 20 ppm and >20 ppm; 6 to 10 ppm \neq >20 ppm.

^b 0 to 5 ppm \neq >20 ppm; 11 to 20 ppm \neq >20 ppm.

^c 0 to 5 ppm \neq 11 to 20 ppm; 6 to 10 ppm \neq 11 to 20 ppm; 11 to 20 ppm \neq >20 ppm.

^d 0 to 5 ppm \neq 6 to 10 ppm; 6 to 10 ppm \neq 11 to 20 ppm.

^e 0 to 5 ppm \neq 11 to 20 ppm and >20 ppm; 6 to 10 ppm \neq 11 to 20 ppm; >20 ppm \neq 0 to 5 ppm, 6 to 10 ppm and 11 to 20 ppm.

* Data are means (\pm standard errors) adjusted for maternal age, number of previous pregnancies and newborn's sex from MANOVA [Wilks lambda = 0.627, $F(15,1356) = 16.62$, $P < 0.0001$].

** Chi-square test.

considered as nonsmokers [16]. In a large sample of pregnant women, Eskenazi et al. [16] found that compared to unexposed nonsmokers' infants, infants of exposed nonsmokers averaged 45 g less, a nonsignificant difference ($P = 0.28$), and birthweight decreased 1 g for every ng/mL of urinary cotinine increase. Study of Secker-Walker et al. [19] and the present one detected higher differences in newborns' birthweight between unexposed and exposed mothers using expired air CO measures. Thus, it seems that expired air CO measure shows a higher sensitivity to predict the unfavorable effects of smoking exposure in newborns.

It is unclear which components of tobacco smoke cause decreased birthweight and perinatal complications. Carbon monoxide seems to have more deleterious effect than nicotine [4]. Fetal hemoglobin traps preferentially carbon monoxide; this decreases the amount of fetal oxyhemoglobin leading to impaired oxygen delivery to the fetal tissues. Carbon monoxide freely crosses the placenta and causes hypoxia in utero [20]. Moreover, carboxyhemoglobin determined in cord blood is more than twice higher in case of maternal smoking than when the mother is a nonsmoker [21]. The endogenous CO production is the highest in pregnancy, and the fetus's CO production is higher than that of a healthy man [20]. Thus, even a small increase in maternal or fetal carboxyhemoglobin concentrations due to smoke exposure may elicit unfavorable effects in the fetus.

To our knowledge, this is the first study that assessed on a prospective way the association of maternal and paternal expired air CO concentrations with clinical indices of birth (heart rate, Apgar score, fetal carboxyhemoglobin). However, this study has several limitations. (a) The investigators who measured expired air CO levels and birth characteristics were not blinded for smoking status which may have biased the measures. (b) Only one expired air CO determination was done during the pregnancy. Although this measure highly correlated with expired air CO results at delivery, sequential expired air CO determinations would give more precise information about the overall smoke exposure. In fact, it has been shown that smoking during the third trimester contributes most to birthweight [14]. (c) Expired air CO of spouses was only measured at the time of delivery; again, sequential measures during the pregnancy would increase the reliability of this measure.

In conclusion, the results of this study suggest that expired air CO can be a suitable measure of smoke exposure and consequent fetal toxicity in pregnant women. This measure is easy to do and cost-effective. We suggest to extend its use in everyday practice: to assess expired air CO in both pregnant women and their spouses to allow a better control of smoking and to target expired air CO concentrations to less than 5 ppm in both women and spouses. The maintaining of this target concentration during the whole duration of pregnancy may substantially improve fetal characteristics at birth.

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