Does *In Utero* Exposure to Heavy Maternal Smoking Induce Nicotine Withdrawal Symptoms in Neonates?

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ABSTRACT

Maternal drug use during pregnancy is associated with fetal passive addiction and neonatal withdrawal syndrome. Cigarette smoking—highly prevalent during pregnancy—is associated with addiction and withdrawal syndrome in adults. We conducted a prospective, two-group parallel study on 17 consecutive newborns of heavy-smoking mothers and 16 newborns of non-smoking, unexposed mothers (controls). Neurologic examinations were repeated at days 1, 2, and 5. Finnegan withdrawal score was assessed every 3 h during their first 4 d. Newborns of smoking mothers had significant levels of cotinine in the cord blood (85.8 ± 3.4 ng/mL), whereas none of the controls had detectable levels. Similar findings were observed with urinary cotinine concentrations in the newborns (483.1 ± 2.5 μ g/g creatinine *versus* 43.6 ± 1.5 μ g/g creatinine; $p = 0.0001$). Neurologic scores were significantly lower in newborns of smokers than in control infants at days 1 (22.3 ± 2.3 *versus* 26.5 ± 1.1 ; $p = 0.0001$), 2 (22.4 ± 3.3 *versus* 26.3 ± 1.6 ; $p = 0.0002$),

and 5 (24.3 ± 2.1 *versus* 26.5 ± 1.5 ; $p = 0.002$). Neurologic scores improved significantly from day 1 to 5 in newborns of smokers ($p = 0.05$), reaching values closer to control infants. Withdrawal scores were higher in newborns of smokers than in control infants at days 1 (4.5 ± 1.1 *versus* 3.2 ± 1.4 ; $p = 0.05$), 2 (4.7 ± 1.7 *versus* 3.1 ± 1.1 ; $p = 0.002$), and 4 (4.7 ± 2.1 *versus* 2.9 ± 1.4 ; $p = 0.007$). Significant correlations were observed between markers of nicotine exposure and neurologic and withdrawal scores. We conclude that withdrawal symptoms occur in newborns exposed to heavy maternal smoking during pregnancy. (*Pediatr Res* 55: 645–651, 2004)

Abbreviations

CO, carbon monoxide
HS, heavy smoker
NS, nonsmoker

Addiction to nicotine is a common feature among HS. The majority of adult smokers are physically dependent on nicotine (1). Physical dependence is responsible for nicotine withdrawal syndrome among self-quitters. In human adults, nicotine withdrawal is characterized by physical, behavioral, and subjective symptoms (2). The neuropharmacologic mechanisms of nicotine withdrawal syndrome are still unclear, but are thought to involve an increased number of nicotine receptors in the CNS (2–4).

Recent surveys indicate that more than 20% of pregnancies in Europe occur in current smokers (5, 6). Approximately 34 to 40% of pregnant women quit or decrease their smoking during gestation in the United States (7).

It is not clear whether fetal passive addiction to nicotine occurs during pregnancy. Indeed, nicotinic acetylcholine receptors are present in the CNS of both animals (8) and humans (9) from the embryonic stage. During smokers' pregnancy, the fetus is chronically exposed to nicotine concentrations that are 15% higher than in the maternal bloodstream (10). The adult metabolism of nicotine is rapid, its half-life being 2 h (11). Studies of nicotine levels in newborns from smoking mothers have shown very low or undetectable levels, suggesting rapid fetal metabolism of nicotine (12).

In most maternity wards, smoking is prohibited during labor. Therefore, acute deprivation of nicotine takes place on maternal admission to the labor room, creating conditions for neonatal nicotine withdrawal.

Withdrawal syndromes in newborns have been characterized with other drugs of abuse, such as opiates and benzodiazepines (13). Conflicting data about nicotine withdrawal in newborns are found in previous studies. Newborns of smoking mothers

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were shown to have impaired performances at days 1 and 2 when compared with newborns of nonsmoking mothers (14). However, these findings were not supported by biologic monitoring of nicotine exposure in mothers and their offspring. Recently, a pilot study described intermediate Finnegan withdrawal scores in a small number of newborns with high urinary cotinine levels (15). In contrast, some clinical studies did not confirm the existence of neonatal nicotine withdrawal symptoms in humans (16) and animals (17).

We wanted to study prospectively the effects of acute cessation of exposure to maternal smoking on normal newborns of HS (>10 cigarettes/d throughout pregnancy) compared with normal newborns of NS, unexposed mothers. We evaluated the effects, if any, of nicotine withdrawal, using a detailed neurologic examination of the newborns, a validated withdrawal score, and a biologic monitoring of exposure to maternal smoking. Given the nicotine half-life, neurologic examination of the newborns was performed on days 1, 2, and 5, whereas Finnegan withdrawal score was recorded every 3 h during days 1, 2, 3, and 4. Maternal smoking was evaluated using a score of physical dependence and a biologic monitoring related to immediate smoking (CO in expired air), recent smoking (urinary cotinine concentration, 48 h), and chronic smoking (salivary thiocyanates, 3 wk). Intrauterine exposure was measured using cord blood cotinine levels and neonatal urinary cotinine concentration (48 h).

METHODS

Population. We recruited 21 HS pregnant women and 18 NS unexposed pregnant women, before delivery, at the antenatal clinic of the Clinique St-Pierre, Ottignies, Belgium. The women were recruited during eight periods of 2 wk, during which nursing staff was available to assess the withdrawal scores. All the pregnancies had been uneventful. All the deliveries took place between 38 and 40 wk of gestation and were considered normal. None of the births occurred by cesarean section. None of the newborns needed resuscitation. One newborn of a smoking mother was excluded because his birth weight was less than 2500 g. Three HS and two NS refused to take part in the study because they wanted an early discharge.

The study protocol was approved by the Ethics Committee of the Clinique St-Pierre, Ottignies. All the mothers gave written informed consent.

Neurologic evaluation. Detailed neurologic examinations were carried out according to widely accepted recommendations (18, 19). All examinations were performed by the same investigator (L.F.), teamed with the pediatric neurologist (C.B.), blind to the smoking status of the mothers. Alertness, spontaneous motility, muscle tone, and primary reflexes were assessed at days 1, 2, and 5.

Alertness was evaluated by the newborn's response to arousal maneuvers and by its spontaneous and provoked motility. Level of alertness, spontaneous motility, eye opening, and tendon reflexes were each scored out of two, the maximum subtotal therefore being eight.

Muscle tone was evaluated as follows. Neck muscle tone was studied using the pull-to-sit maneuver. Passive limb tone

was assessed in quiet repose by adductor angle, popliteal angle, and feet dorsal flexion. Evaluation of trunk tone was performed by ventral and lateral suspensions. Each of these specific maneuvers was scored out of two and the maximum subtotal came to 10.

For primary reflexes, Moro and sucking reflexes were scored out of two, palmar and plantar grasping, tonic neck response, cardinal points reflex, and placing and stepping reactions were scored out of one, and the maximum subtotal came to 10. The maximum possible total for the three categories came to 28.

Finnegan withdrawal score. Finnegan score is a validated score previously designed to evaluate withdrawal symptoms in newborns exposed to opiates during pregnancy (20). The score evaluates the CNS function, the metabolic, vasomotor, and respiratory functions, and the gastrointestinal system (Table 1). Two consecutive scores greater than eight indicate withdrawal syndrome.

Finnegan score was measured every 3 h from day 1 to 4 by the nursing staff. The mean value for each day was calculated.

Monitoring of cigarette smoking. A 7-mL sample of cord blood was obtained from all subjects. Urine samples were obtained from mothers and babies during the first 48 h. A sample of saliva was obtained from the mothers at the same time. CO in expired air was determined in the mothers during the first 72 h after delivery (CO-tester, FIM, Lyon, France). A different investigator (V.G.) administered a smoking questionnaire to the mothers, including a six-item Fagerström score for physical dependence (21) (Table 2) and a personal history of smoking.

Biologic measurements. Blood samples were first treated with trichloroacetic acid (Sigma, St. Louis, MO) to precipitate proteins. Deproteinized plasma or urinary cotinine concentration was then measured after chloroform (Sigma) extraction by HPLC. Analyses were carried out using a Waters Alliance 2690 HPLC separation module (Waters, Milford, MA) equipped with a multiple wavelength detector and a (Millennium 210) processing module. The stationary and mobile phases consisted in a reversed-phase column (Inertsil 5 ODS-3, Chrompack, Bergen op Zoom, The Netherlands,) and in acetonitrile in phosphate buffer, 0.05 M, pH 4.3 (Sigma), respectively (22). The coefficient of variation remained below 5%. The detection limit was 0.010 $\mu\text{g/mL}$. Results were standardized to urinary creatinine measured by Jaffe reaction on Hitachi 747 (Roche, Mannheim, Germany). Discriminated urinary cut-off value between smoker and nonsmoker was fixed at 50 $\mu\text{g/g}$ creatinine.

Salivary thiocyanates were measured by spectrophotometry after addition of ferric chloride (Sigma) according to the method described by Bowler (23).

Statistical methods. Results were expressed as mean $\pm$ SD for normally distributed variables and as geometric means $\pm$ SD for log-normally distributed variables. Log-distributed variables were log-transformed before performing any statistical test. Comparisons between exposed and unexposed newborns were carried out using unpaired *t* test for continuous variables and Fisher exact test *p* value for discrete variables. Neurologic and Finnegan scores were submitted to an ANOVA with a repeated measurement factor (day-to-day measurement)

Table 1. *Finnegan score*

Signs and symptoms	Score	08 h	11 h	14 h	17 h	20 h	23 h	02 h	05 h
High-pitched cry	2								
Continuous high-pitched cry	3								
Sleeps less than 1 h after feeding	3								
Sleeps less than 2 h after feeding	2								
Sleeps less than 3 h after feeding	1								
Hyperactive Moro reflex	2								
Markedly hyperactive Moro reflex	3								
Mild tremors when disturbed	1								
Marked tremors when disturbed	2								
Mild tremors when undisturbed	3								
Marked tremors when undisturbed	4								
Generalized convulsions	5								
Excoriations	1								
Sweating	1								
Fever less than 38.2°C	1								
Fever higher than 38.2°C	2								
Frequent yawning	1								
Mottling	1								
Nasal stuffiness	1								
Sneezing	1								
Respiratory rate over 60 minutes	1								
Respiratory rate over 60 minutes + retractions	2								
Frantic sucking of fists	1								
Regurgitation	2								
Poor feeding	2								
Projectile vomiting	3								
Loose stools	2								
Watery stools	3								
Dehydration	2								
Total score									

Finnegan score for neonatal abstinence, adapted from Finnegan (20) and Suresh (23a).

Table 2. *Fagerström test for nicotine dependence*

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 min	3
	6–10 min	2
	31–60 min	1
	After 60 min	0
2. Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes	1
	No	0
3. Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
4. How many cigarettes/d do you smoke?	10 or fewer	0
	11–20	1
	21–30	2
	31 or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

©Permission to use this scale for other than research purposes should be obtained from K.O. Fagerström (21).

and a grouping factor (exposed or unexposed babies). Significant results led us to perform multiple comparisons, using paired or unpaired *t* tests, without correcting *p* values for multiple testing. Correlations were assessed using the Pearson's cross-product coefficient. All tests were two-sided and *p* values are reported. The statistical significance level was set at 0.05.

RESULTS

Seventeen of the pregnant women were HS, having smoked a mean of 27 ± 11 cigarettes/d before pregnancy. During pregnancy, their smoking habits decreased significantly, with a mean of 18.6 ± 5.7 cigarettes/d ($p = 0.025$). None of the NS

mothers had smoked cigarettes or been exposed to environmental tobacco smoke during pregnancy (Table 3).

A strict nonsmoking policy prevailed both in the maternity ward and in the delivery room. Although smoking mothers did smoke while hospitalized, they refrained from smoking in their rooms and in the maternity ward. Instead, smoking took place in the smoking area of the hospital or outdoors. The newborns were not exposed to environmental smoking during the study. None of the mothers studied used any drug of abuse or alcohol. Their caffeine intake was low and did not depend on whether or not they were smokers.

Smoking habits in mothers. Evaluation of maternal smoking included markers of long-term smoking (salivary thiocyanates, 3 wk), recent smoking (urinary cotinine, 48 h), and of very recent smoking (CO in expired air, 3 h). The duration of smoking and the Fagerström score for physical dependence on nicotine were recorded.

Recent *in utero* exposure of newborns was evaluated using urinary cotinine concentrations in newborns and cord blood cotinine levels. All these variables were specific to smoking mothers and their offspring, and were strongly correlated with one another (Table 4).

Characteristics of the newborns. As previously described, newborns of HS mothers had significantly lower birth weights than newborns of NS, unexposed mothers (3067 ± 274 g versus 3472 ± 286 g; $p = 0.0003$). No significant difference was found with regard to their cranial circumference or to their Apgar score at 1, 5 and 10 min. Ten of the 17 newborns of HS mothers were breastfed, as were 11 of the 16 newborns of NS, unexposed mothers.

Neurologic scores. ANOVA of neurologic scores showed significant interactions, indicating nonsimilar changes in scores between exposed and unexposed newborns ($p < 0.0001$). Changes in repeated neurologic scores in newborns of HS mothers were significant ($p = 0.05$), whereas no significant change was found in repeated neurologic scores of newborns of NS mothers ($p = 0.22$).

On days 1 and 2, newborns of HS mothers had significantly lower scores for muscle tone, primary reflexes, and alertness than newborns of NS mothers. The total neurologic score on both day 1 and 2 was also significantly lower in newborns of HS mothers (Table 5).

On day 5, newborns of HS mothers had significantly lower scores for primary reflexes and alertness than did newborns of NS mothers. Differences persisted for muscle tone but without reaching statistical significance. The total neurologic score on

day 5 was significantly lower in newborns of HS mothers (Table 5).

The total neurologic score on day 1 was significantly lower than on day 5 in newborns of HS mothers, whereas it did not change significantly from day 1 to day 5 in newborns of NS mothers (Table 5).

Finnegan withdrawal scores. Daily values for the Finnegan score were calculated as means of scores recorded every 3 h, every day. ANOVA for repeated measurements demonstrated a significant change in Finnegan scores according to the smoking status of the mother ($p = 0.0004$), whereas no change was found among the various measurements in each group ($p = 0.65$ and 0.64 , respectively).

Mean values for Finnegan scores at days 1, 2, and 4 were significantly higher in newborns exposed to maternal smoking during pregnancy than in unexposed newborns (Table 6).

Statistical analysis of neonatal CNS function and behavior in relation to markers of nicotine withdrawal. Multiple regression analysis of neurologic examination at day 1 of cord blood urinary cotinine, term of pregnancy, and breastfeeding showed that term of pregnancy and breastfeeding were no longer significant determinants for the neurologic examination at day 1 ($p = 0.93$ and 0.88 , respectively), whereas cord blood cotinine level remained significant ($p = 0.0004$).

Newborns' neurologic score at days 1 and 2 demonstrated a negative significant correlation to biologic markers of *in utero* exposure to maternal smoking (Table 7).

We found a significant correlation between Finnegan withdrawal score at day 2 ($r = 0.41$; $p = 0.02$) and at day 4 ($r = 0.41$; $p = 0.02$) and variables of recent neonatal exposure ($\log_{10}$ urinary cotinine in newborn, $\log_{10}$ cord blood cotinine, $\log_{10}$ urinary cotinine in mothers; Table 7).

Finnegan withdrawal score correlated with neurologic score at day 2 ($r = -0.55$; $p < 0.001$).

DISCUSSION

This prospective, two-group parallel study of repeated neurologic examinations and Finnegan withdrawal scores during the first 5 d of life was carried out on 17 consecutive normal newborns from HS mothers, compared with 16 consecutive normal newborns of NS, unexposed mothers. Neurologic scores at days 1, 2, and 5 were significantly lower in newborns of HS mothers than in newborns of NS. The neurologic score improved significantly from day 1 to 5 in newborns of HS mothers, but not in newborns of NS mothers. In addition, at days 1, 2, and 4, the Finnegan withdrawal score was significantly higher in newborns of HS mothers than in newborns of NS mothers. Neurologic scores and Finnegan withdrawal scores were correlated with biologic markers of recent exposure to maternal cigarette smoke and to maternal score of physical dependence to nicotine (Fagerström score).

Nicotine withdrawal syndrome occurs in many adult smokers with a physical dependence on nicotine when they are acutely deprived of nicotine. Nicotine withdrawal syndrome is clinically different in adults from heroin withdrawal syndrome, and has only been reported more recently. The smoking mothers in our study are physically dependent on nicotine, as

Table 3. Characteristics of the mothers

	Smoking mothers (n = 17)	Nonsmoking mothers (n = 16)	p value
Age (y)	30 $\pm$ 6	29 $\pm$ 5	0.69
First pregnancy (n)	3	4	0.68
First child (n)	3	5	0.44
Term of pregnancy (wk)	38.5 $\pm$ 0.5	39.2 $\pm$ 0.7	0.003
No. cigarettes before pregnancy	27 $\pm$ 11	0	
No. cigarettes during pregnancy	18.6 $\pm$ 5.7*	0	

* Paired *t* test on reduction, $p = 0.025$.

Table 4. Maternal smoking characteristics

	Smoking mothers (n = 17)	Nonsmoking mothers (n = 16)	p value
Smoking years (n)*	16 ± 5	...	
Fagerström score*	6.2 ± 1.8	...	
CO in expired air (ppm)†	14.6 ± 2.4	3.3 ± 1.5	0.0001
Salivary thiocyanates† (μg/mL)	236.6 ± 1.3	58.9 ± 1.9	0.0001
Urinary cotinine concentration (μg/g creatinine)†			
Mothers	441.2 ± 2.5	36.1 ± 1.1	0.0001
Newborns	483.1 ± 2.5	43.6 ± 1.5	0.0001
Cord blood cotinine† (ng/mL)	85.8 ± 3.4	Under the detection limit	

* Values are mean ± SD.

† Values are geometric mean ± SD.

Table 5. Neurologic scores of newborn babies

Time	Score	Smoking mother (n = 17)	Nonsmoking mother (n = 16)	p value
Day 1	Muscle tone	7.9 ± 1.5	9.5 ± 0.7	0.001
	Primary reflexes	7.5 ± 0.9	9.0 ± 0.7	0.0001
	Alertness	6.8 ± 1.4	7.9 ± 0.2	0.004
	Total neurologic score	22.3 ± 2.3	26.5 ± 1.1	0.0001
Day 2	Muscle tone	8.2 ± 1.7	9.2 ± 1.0	0.05
	Primary reflexes	7.5 ± 1.3	9.2 ± 0.7	0.0001
	Alertness	6.7 ± 1.1	7.7 ± 0.5	0.001
	Total neurologic score	22.4 ± 3.3	26.3 ± 1.6	0.0002
Day 5	Muscle tone	8.6 ± 1.5	9.1 ± 1.1	0.22
	Primary reflexes	8.3 ± 1.2	9.4 ± 0.5	0.002
	Alertness	7.4 ± 0.7	7.9 ± 0.2	0.01
	Total neurologic score	24.3 ± 2.1*	26.5 ± 1.5	0.002

* Neurologic score vs day 1, $p = 0.05$.

Table 6. Finnegan score

Finnegan score	Smoking mother (n = 17)	Nonsmoking mother (n = 16)	p value
Day 1	4.5 ± 2.1	3.2 ± 1.4	0.05
Day 2	4.7 ± 1.7	3.1 ± 1.1	0.002
Day 3	3.8 ± 1.5	3.0 ± 1.3	0.13
Day 4	4.7 ± 2.1	2.9 ± 1.4	0.007

demonstrated by their high Fagerström scores. Fetal exposure is demonstrated by the presence of cotinine in the cord blood and in the newborns' urine.

Withdrawal syndrome in newborns passively addicted *in utero* to substances of abuse has been well characterized with opiates. Previous studies have shown that the withdrawal syndrome was more likely to occur in newborns of heroin-addicted mothers if the maternal dose had been high, if the last dose had been taken 24 h before the time of birth, if the mother had been a long-term addict, and if the infant was born at term (19). In our study population, maternal dose had been high (mean of 27 cigarettes/d before pregnancy, 18.6 cigarettes/d during pregnancy) with long-term addiction (mean of 16 y). In addition, the last dose had been taken less than 24 h before birth, as suggested by the high levels of cotinine measured in the cord blood.

Indeed, nicotine has been present at all stages of development of the CNS of newborns of nicotine-addicted mothers. Withdrawal from a substance that has been present during CNS development is likely to be different from withdrawal in adults, in which the drug has been initiated in a fully developed brain. Given the high prevalence of smoking during pregnancy, we know that no dramatic symptoms comparable to heroin withdrawal take place in newborns of smoking mothers. The accuracy of our observations may also be limited by the instrument used to evaluate withdrawal in newborns, which has been designed to evaluate opiate withdrawal.

Recent data from fetal behavioral studies indicate that fetal activity is significantly lower in fetuses chronically exposed to maternal smoking than in unexposed control fetuses (24). In addition (25), fetuses exposed to nicotine have been shown to have an altered neurobehavioral profile. The effect of acute cessation of exposure to maternal smoking on fetal behavior has not been investigated. Recent studies of cocaine-exposed newborns have regarded their neurobehavioral abnormalities as persistent cocaine effect rather than withdrawal symptoms (13). However, the short half-life of nicotine and the significant improvement of the neurologic score between days 1 and 5 only in nicotine-exposed babies suggest a withdrawal process.

The serial neurologic examinations are of major value, when carefully and thoughtfully performed by the same clinician. Even if the predictive power of isolated neurologic signs in the newborn period is not great, the value of combining abnormal signs has been fully recognized in previous studies (26).

Because 10 of the 17 smoking mothers were breastfeeding, the urinary cotinine concentration in their newborn babies was possibly influenced by digestive absorption of nicotine present in mother's milk. Previous studies carried out in newborns found no correlation between nicotine and cotinine concentrations in the newborn's urine samples and the amount of nicotine present in the mother's milk (27). In addition, a supplement of nicotine would decrease any withdrawal effect. In this study, the influence of nicotine supply through breastfeeding was shown to be not significant using multiple linear regression.

Although most smoking mothers had smoked their first cigarette a few hours after birth, as suggested by their CO level in expired air (28), the nonsmoking policy of the maternity ward was carefully enforced, ensuring that the mothers did not

Table 7. Correlations between clinical characteristics of newborns (neurologic score and Finnegan withdrawal score) and markers of fetal exposure to nicotine and of maternal smoking

Monitoring maternal smoking	Neurologic day 1	Neurologic day 2	Neurologic day 5	Finnegan day 1	Finnegan day 2	Finnegan day 3	Finnegan day 4
Cotinine*							
Cord blood	-0.753 ($p < 0.001$)	-0.585 ($p < 0.001$)	-0.520 ($p < 0.001$)	0.284 ($p = 0.14$)	0.529 ($p = 0.002$)	0.316 ($p = 0.09$)	0.465 ($p = 0.01$)
Urinary baby	-0.648 ($p < 0.001$)	-0.595 ($p < 0.001$)	-0.523 ($p = 0.002$)	0.185 ($p = 0.31$)	0.471 ($p = 0.006$)	0.315 ($p = 0.07$)	0.441 ($p = 0.01$)
Urinary mother	-0.606 ($p < 0.001$)	-0.605 ($p < 0.001$)	-0.529 ($p = 0.002$)	0.146 ($p = 0.43$)	0.489 ($p = 0.004$)	0.172 ($p = 0.35$)	0.433 ($p = 0.01$)
Thiocyanates*	-0.658 ($p < 0.001$)	-0.500 ($p = 0.005$)	-0.476 ($p = 0.009$)	0.247 ($p = 0.20$)	0.427 ($p = 0.02$)	0.187 ($p = 0.34$)	0.419 ($p = 0.02$)
salivary, mother							
CO*—mother	-0.680 ($p < 0.001$)	-0.683 ($p < 0.001$)	-0.461 ($p = 0.007$)	0.078 ($p = 0.69$)	0.398 ($p = 0.02$)	0.087 ($p = 0.63$)	0.324 ($p = 0.07$)
Fagerström score—mother	-0.689 ($p < 0.001$)	-0.628 ($p < 0.001$)	-0.421 ($p = 0.01$)	0.294 ($p = 0.09$)	0.533 ($p = 0.001$)	0.138 ($p = 0.45$)	0.420 ($p = 0.01$)

* Expressed on a log₁₀ scale.

smoke during labor and that the newborns were not exposed to environmental tobacco smoke. The mean duration of labor was higher than 8 h. The half-life of maternal COHb being about 3 h (29), that of the newborn is considered longer (30); therefore a possible influence of COHb on neurologic score at day 1 cannot be excluded. In this study, we did not measure COHb in the cord blood. However, data from previous studies, measuring maternal and fetal COHb during pregnancy, indicate a mean fetal level of $4.5 \pm 3.1\%$ and a ratio of fetal to maternal COHb of 1.32 ± 0.61 , and demonstrate strong direct associations of fetal and maternal levels of COHb and cotinine (31).

The differences in neurologic scores in the newborns might have been influenced by the difference of 5 d in the term of pregnancy between the two groups; this factor was not a significant determinant of neurologic score when compared with markers of nicotine exposure, using multiple linear regression.

Neurologic scores and Finnegan withdrawal scores in newborns of HS mothers do not normalize at day 5. However, we do not have information about the evolution of Finnegan score and neurologic score after the fifth day of life, because the mothers and their babies were discharged from the maternity ward on the fifth day after birth. Thus, we do not have information about the length of nicotine withdrawal symptoms in neonates.

The small number of neonates and mothers in this study did not allow us to include other important variables in our analysis, such as socioeconomic determinants of maternal smoking. The mothers' level of education was, however, comparable between both groups.

CONCLUSIONS

Thus, our data strongly suggest that nicotine withdrawal symptoms, even discrete, are present in newborns of HS mothers. This conclusion supports the hypothesis that fetal passive addiction to nicotine occurs during pregnancy in HS.

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