Relationship of Maternal Snuff Use and Cigarette Smoking With Neonatal Apnea

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KEY WORDS
nicotine, prenatal, gestation, exposure, respiration, newborn, smokeless tobacco

ABBREVIATIONS
SIDS—sudden infant death syndrome
NRT—nicotine-replacement therapy
SGA—small for gestational age

Drs Cnattingius and Wickström had the original idea for the study, and all authors contributed to the design of the study; Dr Gunnerbeck performed the analyses under supervision of Drs Wickström and Cnattingius and wrote the first draft of the manuscript; and all authors made substantial contributions to the interpretation of results and manuscript revision.

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WHAT'S KNOWN ON THIS SUBJECT: Maternal smoking is associated with harmful effects on the newborn: preterm birth, fetal growth restriction, and sudden infant death syndrome. Much less is known about the effects of smokeless tobacco, and nicotine-replacement therapy is recommended as a means of smoking cessation during pregnancy.

WHAT THIS STUDY ADDS: Maternal snuff use (including predominantly nicotine) is associated with higher risk of neonatal apnea than smoking (containing nicotine and combustion products). Snuff use should not be regarded as safe during pregnancy.

abstract

FREE

BACKGROUND: Maternal smoking is associated with disturbed cardiorespiratory control in the infant. Despite lacking knowledge of whether the harmful effects of smoking are caused by combustion products in tobacco smoke or by nicotine, it has been argued that nicotine-replacement therapy during pregnancy is safer than smoking.

OBJECTIVE: The goal of this study was to investigate if the disturbances in cardiorespiratory control associated with maternal smoking are also seen in infants prenatally exposed to snuff. We hypothesized that prenatal nicotine exposure (via moist snuff) causes disturbances in autonomic control and thereby increases the risk of apnea in the newborn.

METHODS: In a nationwide Swedish cohort study, we studied associations between maternal tobacco use during pregnancy and neonatal apnea. Of 609 551 live-born singleton infants, 7599 were born to snuff-using mothers, 41 391 and 16 928 were born to light (1–9 cigarettes per day) and heavy (≥10 cigarettes per day) smokers, respectively. Logistic regression was used to calculate odds ratios, using 95% confidence intervals.

RESULTS: Compared with infants of nontobacco users, infants with prenatal exposure to snuff were at an increased risk of apnea even after adjustment for differences in gestational age (odds ratio: 1.96 [95% confidence interval: [1.30–2.96]) Smoking was associated with increased risk of apnea before, but not after, adjusting for gestational age.

CONCLUSIONS: Snuff use during pregnancy is associated with a higher risk of neonatal apnea than smoking. Maternal use of snuff or nicotine-replacement therapy cannot be regarded as an alternative to smoking during pregnancy. *Pediatrics* 2011;128:503–509

Smoking during pregnancy may be the most important preventable risk factor for the newborn and is causally associated with fetal growth restriction and probably also with preterm birth and sudden infant death syndrome (SIDS).[1,2] A disturbed cardiorespiratory control is believed to be part of the mechanism behind SIDS, and epidemiologic studies reveal that maternal smoking also increases risks of other disturbances in the cardiorespiratory system, such as apnea.[3,4] Despite lacking knowledge of whether these harmful effects are generated by nicotine or by combustion products in tobacco smoke, nicotine-replacement therapy (NRT) is commonly regarded as safer than smoking and is sometimes recommended as a means of smoking cessation for pregnant women.[5,6]

Internationally, public health researchers debate whether Swedish snuff, with lower levels of nitrosamines but higher levels of nicotine than tobacco smoke, should be recommended as a harm reduction drug for smoking cessation.[7–10] The rate of female snuff users has more than tripled during the last decade in Sweden, and the use of smokeless tobacco has increased globally, especially among women of childbearing age.[11,12] There are few studies of the effects of snuff use during pregnancy, but a recently published study revealed an association between maternal snuff use during pregnancy and an increased risk of stillbirth.[13]

By studying snuff use and smoking during pregnancy, our goal was to differentiate between effects mainly caused by nicotine (snuff) and those linked to combustion products in tobacco smoke. If nicotine caused the disturbances in the neural control of the cardiorespiratory system seen in newborns of smoking mothers,[14] we would expect similar effects in infants prenatally exposed to snuff.

The high number of young women using snuff in Sweden and the prospectively collected data on snuff (and cigarette) use in the nationwide Swedish Medical Birth Register enabled us to study snuff use during pregnancy as a model for investigating the effects of prenatal nicotine exposure in humans. We hypothesized that prenatal nicotine exposure, by causing disturbances in the control of the autonomic nervous system, would increase the risk of apnea in the newborn.

METHODS

The Swedish Medical Birth Register, held by the National Board of Health and Welfare, is a population-based register that contains data on >98% of all births in Sweden, including demographic data, information on reproductive history, pregnancy, delivery, and the neonatal period.[15] Diagnoses, including neonatal complications, are classified since 1997 according to the *International Classification of Diseases, 10th Revision* and are noted by the responsible physician at discharge from hospital.

By means of each individual's unique personal identification number, the birth register can be linked with other Swedish data sources.[16] Through linkage with the education register and the register of total population, both held by Statistics Sweden, we obtained information about the mother's level of education and country of birth.

Study Population

From 1999 to 2006, there were 610 346 singleton infants recorded in the Swedish Medical Birth Register of mothers born in the Nordic countries (ie, Denmark, Finland, Iceland, Norway, Sweden). Information on gestational age at birth was available for 609 551 infants. Preferably, gestational age was determined by ultrasound scan between weeks 17 to 20 of gestation. If no ultrasound scan was available, the first day of the last menstrual period was used to calculate gestational age. In Sweden, all women are offered an ultrasound scan to estimate gestational age, usually around week 17 of gestation. Ninety-five percent of women accept this offer.[17]

The study was approved by the research ethics committee at the Karolinska Institutet (No. 2009/1726–32).

Exposures

Antenatal booking occurs before week 15 of gestation in >95% of all pregnancies.[18] Information about maternal characteristics (eg, height, parity, tobacco use) are collected at this first visit. Tobacco use is categorized as nonuse, snuff use, moderate smoking (1–9 cigarettes per day), or heavy smoking (≥10 cigarettes per day). In the study population, there were 503 460 (82.6%) nonusers, 7599 (1.2%) snuff users, 41 391 (6.8%) light smokers, 16 928 (2.8%) heavy smokers, and 481 (0.08%) who reported that they used both snuff and cigarettes (dual users). In 39 692 women (6.5%), there was no information on tobacco use. Information about maternal age was obtained at discharge from the hospital after delivery. Through linkage with the education register, information was obtained regarding number of years of formal education completed as of January 1, 2008. The mothers' level of education was categorized as ≤9, 10 to 12, or ≥13 years.

Small for gestational age (SGA) was defined as a birth weight >2 SDs below the mean birth weight for gestational age according to the gender-specific Swedish fetal growth curve.[19] Gestational age was stratified into very preterm (≤31 completed weeks), moderately preterm (32–36 weeks), term (37–41 weeks), and postterm (≥42 weeks) birth.

TABLE 1 Tobacco Use During Pregnancy and Rates (%) of Maternal and Neonatal Characteristics: Single Births in Sweden, 1999–2006 ($N = 609\,551$)

Maternal and Neonatal Characteristics	Nonuser ($n = 503\,460$)	Snuff User ($n = 7599$)	Smoker		Dual User ($n = 481$)
			1–9 Cigarettes per d ($n = 41\,391$)	≥10 Cigarettes per d ($n = 16\,928$)	
Age, ≤19 y	1.1	1.9[a]	6.4[a]	3.6[a]	4.2[a]
Height, ≤159 cm	8.6	11.3[a]	11.8[a]	12.4[a]	13.5[b]
Multiparity, ≥4	4.2	7.3[a]	8.0[a]	18.5[a]	10.0[a]
Education, ≤9 y	5.6	11.3[a]	27.0[a]	34.0[a]	25.6[a]
Cesarean delivery	15.4	18.2[a]	16.5[a]	16.6[a]	16.4
Gestational age, ≤36 wk	4.6	5.8[a]	6.1[a]	7.3[a]	5.6
SGA[c]	2.2	2.4	4.7[a]	5.8[a]	5.6[a]

Pregnancies with missing information: 39 692 for tobacco, 13 633 for height, and 9290 for education.

[a] $P < .0001$ versus nonusers.

[b] $P < .001$ versus nonusers.

[c] SGA was defined as >2 SDs below the mean birth weight for gestational age according to the gender-specific Swedish fetal growth curve.[19]

Outcomes

We studied the effects of prenatal nicotine exposure in the form of cigarettes and smokeless tobacco (snuff) on conditions related to respiratory control in the newborn. An initial assessment of the health of the newborn was made by the responsible doctor directly after birth and continuously during the hospital stay, at either the maternity or neonatal ward. A final assessment was also made before discharge from the hospital. Diagnoses were noted by the responsible pediatrician at discharge. *International Classification of Diseases, 10th Revision* codes P28.2 ("cyanotic attacks of newborn"), P28.3 ("primary sleep apnea of newborn"), and P28.4 ("other apnea of newborn") were used to diagnose neonatal apnea. We chose to study these diagnoses together as "unspecified apnea" (P28.2, P28.3, and P28.4).

Statistical Analyses

Unconditional logistic regression analyses were used to estimate associations between tobacco exposures and risks of apnea in the newborn, using the PROC GENMOD procedure. Infants whose mothers had missing information on tobacco consumption were excluded from analysis. Infants of dual users were too few to be analyzed. Odds ratios, presented with 95% confidence intervals, were calculated. The risks of apnea were estimated in snuff users, light smokers, and heavy smokers, with nontobacco users as the reference group. In the first adjusted model, we considered maternal characteristics, such as maternal age, height, parity, and years of formal education, as potential confounders. We also wanted to investigate whether possible risks related to tobacco use were mediated by delivery complications or birth outcomes. In the final model, we therefore also adjusted for gender of the newborn, gestational age, SGA, and method of delivery. Method of delivery was categorized into presence or absence of cesarean delivery. To test for a possible interaction between gender and tobacco, the likelihood ratio test was used to compare the logistic model with and without interaction variable. The χ^2 test was used for statistical analyses. All analyses were performed by using SAS 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Compared with nontobacco users, tobacco-using mothers were to a larger extent teen-aged mothers, of short stature, multiparous (ie, at least 4 childbirths), and less educated (≤9 years of education) (Table 1). These associations were generally most pronounced among heavy smokers and dual users.

Compared with newborns of nontobacco users, rates of SGA were substantially higher in newborns of smokers and in dual users but not significantly higher in infants of snuff users. Rates of preterm birth (≤36 weeks) were also significantly higher in newborns of snuff users and in smokers compared with nonusers. Compared with nontobacco users, the rates of cesarean delivery were slightly increased in snuff users and smokers (Table 1).

Table 2 presents associations between maternal characteristics and unspecified neonatal apnea. High maternal age (≥35 years) and short maternal stature (≤159 cm) were associated with increased risks of apnea after adjusting for maternal confounders (Table 2, adjusted model 1). These risks were reduced and nonsignificant when we also adjusted for mode of delivery and birth outcomes (Table 2, adjusted model 2). In contrast, the U-shaped association between parity and apnea, with infants of primiparous and multiparous (≥4) mothers being at higher risk, remained—although attenuated—in the adjusted models. Compared with infants born at term, moderately preterm infants (32–36 weeks) faced a 10-fold increased risk of apnea, whereas the corresponding increased risk among very preterm infants (≤31 weeks) was 150-fold. Infants delivered

TABLE 2 Maternal and Neonatal Characteristics and Risk of Unspecified Neonatal Apnea: Single Births in Sweden, 1999–2006 ($N = 609\,551$)

	Apnea				
	No.	Rate/1000	Odds Ratio (95% Confidence Interval)		
			Crude	Adjusted Model 1[a]	Adjusted Model 2[b]
Maternal characteristics					
Maternal age, y					
≤19	25	2.7	1.56 (1.01–2.41)	1.25 (0.79–1.99)	1.17 (0.74–1.87)
20–24	116	1.7	Reference	Reference	Reference
25–29	292	1.6	0.91 (0.73–1.13)	1.08 (0.86–1.35)	0.98 (0.78–1.23)
30–34	291	1.4	0.81 (0.65–1.00)	1.05 (0.82–1.33)	0.90 (0.71–1.15)
≥35	207	2.0	1.13 (0.90–1.42)	1.46 (1.13–1.88)	1.11 (0.85–1.43)
Height, cm					
130–159	108	2.2	1.35 (1.10–1.65)	1.31 (1.0–1.61)	1.06 (0.86–1.31)
160–174	716	1.6	Reference	Reference	Reference
≥175	78	1.3	0.79 (0.63–1.00)	0.81 (0.64–1.02)	0.94 (0.74–1.19)
Missing	29	2.1			
Parity					
1	521	2.0	1.70 (1.48–1.95)	1.80 (1.55–2.08)	1.30 (1.12–1.51)
2–3	340	1.2	Reference	Reference	Reference
4–9	70	2.5	2.07 (1.60–2.68)	1.60 (1.21–2.11)	1.47 (1.10–1.95)
Education, y					
≤9	88	1.9	1.32 (1.04–1.66)	1.16 (0.89–1.52)	0.95 (0.73–1.25)
10–12	463	1.7	1.16 (1.01–1.33)	1.12 (0.97–1.30)	1.03 (0.89–1.20)
≥13	364	1.5	Reference	Reference	Reference
Missing	16	1.7	—	—	—
Birth characteristics					
Cesarean delivery					
Yes	379	4.3	3.74 (3.28–4.26)	—	1.19 (1.02–1.40)
No	552	1.1	Reference	—	Reference
Gender					
Male	517	1.8	1.18 (1.04–1.34)	—	1.12 (0.97–1.28)
Female	414	1.5	Reference	—	Reference
Gestational age, wk					
≤31	359	102.9	156 (135–182)	—	139 (115–167)
32–36	175	7.3	10.04 (8.38–12.04)	—	9.49 (7.88–11.43)
37–41	362	0.7	Reference	—	Reference
≥42	35	0.7	0.98 (0.69–1.39)	—	0.93 (0.65–1.34)
SGA[c]					
Yes	117	8.4	5.76 (4.74–6.99)	—	Reference
No	814	1.5		—	0.85 (0.68–1.07)

Pregnancies with missing information for tobacco use ($n = 39\,692$) were excluded from the analyses as well as dual users, which were too few ($n = 480$) to give raise to any cases.
[a] Model 1 was adjusted for maternal age, height, parity, education, and tobacco use.
[b] Model 2, in addition to maternal age, height, parity, education, and tobacco use, was adjusted for cesarean delivery, gender, gestational age, and SGA.
[c] SGA was defined as >2 SDs below the mean birth weight for gestational age according to the gender-specific Swedish fetal growth curve.[19]

by cesarean delivery had an almost fourfold increase in risk, which largely could be explained by a larger proportion of infants with short gestational age and SGA infants in this group. The more than fivefold increased risk of apnea among SGA infants was almost entirely explained by increased risk of shorter gestational age. The overall dominating risk of neonatal apnea was preterm birth.

In the univariate analysis, there was a more than twofold increased risk of apnea in infants born to snuff users compared with nontobacco users, whereas there was a 50% increase in risk among infants born to smokers. After adjusting for maternal characteristics (Table 3, adjusted model 1), the risks of apnea among infants of snuff users and moderate and heavy smokers were slightly attenuated. To investigate whether these tobacco-related risks were mediated by fetal growth, gestational age, or mode of delivery, we also adjusted for gestational age, SGA, cesarean delivery, and gender of the infant (Table 3, adjusted model 2). Compared with nontobacco users, there was still an almost twofold risk of apnea among infants of snuff users, whereas infants of light or heavy smokers were no longer at increased risk of apnea. There was no interaction between gender and tobacco use (yes/no) with respect to risk of apnea ($P > .05$).

DISCUSSION

This population-based cohort study revealed that infants of snuff users face a doubled risk of unspecified neonatal

TABLE 3 Mothers' Tobacco Use During Pregnancy and Risk of Apnea: Single Births in Sweden, 1999–2006

Tobacco Use	Apnea				
	No.	Rate/1000	Odds Ratio (95% Confidence Intervals)		
			Crude	Adjusted Model 1[a]	Adjusted Model 2[b]
Nonuser	771	1.5	Reference	Reference	Reference
Snuff user	26	3.4	2.24 (1.52–3.32)	2.15 (1.44–3.20)	1.96 (1.30–2.96)
Cigarette smoker					
1–9 cigarettes per d	94	2.2	1.48 (1.20–1.84)	1.31 (1.04–1.65)	1.08 (0.85–1.37)
≥10 cigarettes per d	40	2.4	1.54 (1.12–2.12)	1.49 (1.07–2.08)	1.08 (0.76–1.52)

Pregnancies with missing information for tobacco use ($n = 39\,692$) were excluded from the analyses as well as dual users, which were too few ($n = 480$) to give raise to any cases. The rate of apnea among infants to mothers with missing information of tobacco use was 2.7 per 1000.

[a] Model 1 was adjusted for maternal age, height, parity, education, and tobacco use.

[b] Model 2s, in addition to maternal age, height, parity, education, and tobacco use, was adjusted for cesarean delivery, gender, gestational age, and SGA.

apnea. A lower risk increase was seen in infants prenatally exposed to maternal tobacco smoke. In contrast to risks in infants of snuff users, these risks vanished after adjustment for gestational age, SGA, and cesarean delivery.

Neonatal apnea may be a sign of disturbed control of the autonomic nervous system. The most common cause of neonatal apnea is an immature nervous system, and the risk of apnea increases with decreasing gestational age. Furthermore, SIDS is correlated to an increased incidence of apnea and disturbances in the cardiorespiratory control system.[20–22] The underlying mechanisms have not yet been clarified, but maternal tobacco smoke and preterm birth are strong risk factors for SIDS.[22] Our hypothesis is that nicotine causes disturbances in the autonomic nervous system in infants prenatally exposed to tobacco smoke. Findings from earlier studies of maternal smoking during pregnancy, as well as animal studies with prenatal nicotine exposure, support this hypothesis.[23–25]

Preterm infants and infants prenatally exposed to nicotine reveal similar disturbances in the neural control of the cardiorespiratory system, with a heightened vascular, cardiac, and blood pressure reactivity.[26] This finding represents an effect of immaturity in the premature infant and a developmental programming effect of a neurotoxic substance, nicotine, in the nicotine-exposed infant. Activation of nicotinic acetylcholine receptors during vulnerable periods of prenatal development may lead to changes in the cellular programming.[27,28] In animal studies, prenatal exposure to pure nicotine indicates disturbances in the control of the cardiorespiratory system, with an increased frequency of apnea during sleep, decreased arousability and a blunted cardiorespiratory response to hypoxia, higher breathing frequency, and lower tidal volume during the neonatal period.[29,30] Our finding of an increased risk of infant apnea, as a sign of disturbed control of the cardiorespiratory system, correlates well with similar findings in animal studies of prenatal nicotine exposure. Huang et al[31] found an increased frequency of apneas during sleep in a group of prenatally nicotine-exposed rat pups during the first 2 postnatal days but not at postnatal day 6. Altered breathing patterns with increased respiratory frequency and lower tidal volume were only observed after 10 to 18 postnatal days. Both epidemiologic studies and animal studies indicate different early and long-term effects of prenatal nicotine exposure.[26,31] In our study, however, we were only assessing the early effects of prenatal nicotine exposure on the infant.

Previous epidemiologic studies of infants prenatally exposed to tobacco smoke have demonstrated an increased frequency of apnea during sleep and decreased arousability.[32,33] We found that the smoking-related increased risk of apnea was explained by the increased risk of preterm birth and SGA associated with smoking. Surprisingly, the risk of apnea in infants of snuff users was not only higher than that of smokers, but the risk also remained after adjustment for gestational age and size at birth. These findings imply that snuff might have a different mechanism of action than tobacco smoke. It has been reported that the smoking-related risks of preterm birth and SGA are substantially higher than corresponding risks among snuff users.[13,34,35] Swedish snuff (snus) contains no combustion products but higher levels of nicotine and lower concentrations of nitrosamines than cigarettes. It also differs from US moist snuff, which contains less nicotine but higher levels of nitrosamines.[8]

The effects of Swedish snuff can be compared with those of NRT in many ways. Both snuff and NRT mainly contain nicotine, with the nicotine level remaining continuously high during use. Whereas smoking generates peaks of high plasma nicotine levels (duration: 30 minutes) intermittently throughout the day, snuff and NRT have a slower release, with peak nicotine levels having a duration of 1.5 hours.[36] The higher nicotine levels and the more

continuous exposure on the nicotinic acetylcholine receptors in snuff users, compared with the intermittent exposure in smokers, may be of importance for the differences in risks of apnea found between infants of snuff users and smokers.

A major strength of the present study is the nationwide study design, and the prospectively collected information on tobacco use in early pregnancy should eliminate the risk of recall bias. Also, the study population is fairly homogenous, with only infants of mothers born in the Nordic countries included. Adjustment for maternal characteristics and the use of standardized records should reduce the potential for confounding by unmeasured sociodemographic factors.

Events of apnea in awake infants are often explained by esophageal reflux or other vagal stimuli, whereas sleep apnea is associated with disturbances in the neural control of the cardiorespiratory system. Infant apnea is defined by the American Academy of Pediatrics as "an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, and/or marked hypotonia."[37]

A weakness of this study is the uncertainty about the diagnosis of apnea itself. The assessment of apnea was made when the infant was in the hospital, and preterm infants are much more often subjected to neonatal care than term infants. Neonatal apnea is strongly correlated to prematurity. Thus, the increased monitoring of preterm infants may have biased the association between gestational age and apnea. There might also be an underreporting of the diagnosis of apnea in both preterm and otherwise healthy infants not treated at the neonatal ward. However, it seems unlikely that the validity of the diagnosis should differ with respect to prenatal tobacco exposure.

Because this is a register study from the Swedish Medical Birth Register, we only have access to the diagnoses until the infant and mother are discharged from the hospital. Infants with severe diseases may also be missed because of change of hospitals. We were only able to study the early effects of prenatal nicotine exposure and have no knowledge about long-term effects of prenatal exposure. We do not know if infants with the diagnosis of apnea in the neonatal period run a greater risk of developing sleep apnea syndrome, acute life-threatening events, or SIDS, nor if there is an otherwise higher morbidity among these infants.

Other weaknesses are correlated to the design of a population-based register study. We have only self-reported data on tobacco exposure from the first antenatal visit and no information of cotinine levels. There is a risk of underreporting because of extensive knowledge about the negative effects of smoking during pregnancy. Self-reported information on smoking during pregnancy is, however, reported as valid in Sweden,[38] whereas there is no such information on snuff use. Smokers were divided into light and heavy smokers, but we have no knowledge about level of consumption or pattern of snuff use. Because of the high rate of missing information on tobacco use in late pregnancy, we have only used information on tobacco use at antenatal booking in our analyses.

CONCLUSIONS

Our study indicates that snuff use during pregnancy is associated with an almost doubled increased risk of neonatal apnea, a finding that is consistent with animal studies of prenatal nicotine exposure. Our results suggest that nicotine is also responsible for these effects in humans, and that alterations in neural programming may be an underlying mechanism. In this perspective, snuff use and NRT should not be regarded as being safer than smoking during pregnancy.

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