

Influence of smoking and snuff cessation on risk of preterm birth

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Abstract The mechanisms by which antenatal smoking exposure increases the risk of preterm birth remain unknown. Swedish oral moist snuff contains quantities of nicotine comparable to those typically absorbed from cigarette smoking, but does not result in exposure to the products of combustion, for example carbon monoxide. In a nationwide study of 776,836 live singleton births in Sweden from 1999 to 2009, the authors used multiple logistic regression models to examine associations between cessation of smoking and Swedish snuff use early in pregnancy and risk of preterm birth (before 37 weeks). Compared with non-tobacco users both before and in early pregnancy, the

adjusted odds ratios (OR), 95 % confidence interval (CI) were OR = 0.92, 95 % CI 0.84–1.01, for women who stopped using snuff, and OR = 0.90, 95 % CI 0.87–0.94, for women who stopped smoking. In contrast, continued snuff use and smoking were associated with increased risks of preterm birth (adjusted OR = 1.29, 95 % CI 1.17–1.43, adjusted OR = 1.30, 95 % CI 1.25–1.36, respectively). The snuff and smoking-related risks were, if anything, higher for very (before 32 weeks) than moderately (32–36 weeks) preterm birth, and also higher for spontaneous than induced preterm birth. These findings suggest that antenatal exposure to nicotine is involved in the mechanism by which tobacco use increase the risk of preterm birth.

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Introduction

Although infant mortality in preterm born infants has markedly decreased during recent decades, preterm birth (before 37 weeks) is still the leading cause of infant morbidity and mortality in high income countries. Today, the majority of infant deaths occur among very preterm born infants, i.e., infants born before 32 weeks of gestation.

Smoking during pregnancy is associated with increased risk of preterm birth, and risks are generally higher for very (before 32 weeks) than moderately (32–36 weeks) preterm birth [1, 2]. The mechanisms by which smoking increases risk of preterm birth are not fully known. Swedish oral moist snuff, which is a kind of smokeless tobacco, also increases the risk of preterm birth [3, 4]. Snuff contains quantities of nicotine comparable to those typically absorbed from cigarette smoking, but does not result in

exposure to the products of combustion, for example carbon monoxide [5]. These findings indicate that nicotine may increase the risk of preterm birth.

Globally, the use of smokeless tobacco has increased, predominantly in women in childbearing age [3, 4]. Smokeless tobacco has been advocated as a less harmful alternative to smoking [6]. The tobacco industry is now attempting to actively recruit new user groups of snuff among young people and women, by increasing the advertisement in general (rather than male) magazines and marketing flavored snuff products [7].

If there is a causal relationship between smoking or snuff use and risk of preterm birth, those who stop smoking or stop using snuff before or early in pregnancy should reduce their risks. Studies from the Netherlands and New Zealand suggest the possibility for reversible adverse effects on preterm birth by smoking cessation in early pregnancy [8, 9]. In a randomized controlled trial, infants born to women who stopped smoking during pregnancy had longer gestation periods than did infants whose mothers continued to smoke throughout pregnancy [10]. There has been no study to examine the association between change of snuff habits and risk of preterm birth.

The Swedish Medical Birth Register gave access to nation-wide information about tobacco habits 3 months before and in early pregnancy for the years 1999–2009. We used this information to perform a large population-based study to evaluate whether cessation of smoking or snuff use in early pregnancy reduce the risk of preterm birth.

Materials and methods

Study population

Information from the Swedish Medical Birth Register was used to define the study population. The Birth Register contains data on more than 99 % of all births in Sweden, including demographic data, information on reproductive

history, and complications that occur during pregnancy, delivery, and the neonatal period [11, 12]. Snuff use is very rare among women born outside the Nordic countries (i.e. women born in other countries than Sweden, Denmark, Norway, Iceland, and Finland). To increase the homogeneity of the study population, we only included women born in the Nordic countries who delivered a live singleton infant in Sweden during the years 1999–2009 ($n = 872,249$).

In Sweden, gestational age is assessed by ultrasound scans in 97 % of women, usually around the 17th weeks of gestation [13]. If no early second-trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery. We excluded 827 pregnancies with missing information on gestational age at delivery.

At the time of registration for antenatal care, which occurs before 15 weeks of gestation for more than 95 % of the pregnancies [14], information on tobacco use at 3 months before pregnancy and present tobacco use is collected by midwives [12]. Information about smoking has been recorded since 1983 and information about snuff use since 1999. Women are categorized as non-tobacco users, snuff users, smokers, and combined snuff and cigarette users.

Of all 871,422 women, information on both pre-pregnancy and early pregnancy tobacco habits was available at for 782,300 women (89.8 %; Table 1). Among these women, 607,430 women (77.6 %) were non-tobacco users both 3 months before pregnancy and in early pregnancy. Among 20,577 women reporting that they used snuff 3 months before pregnancy, the majority (58.2 %) had stopped using snuff before the first visit to antenatal care. Similarly, among 151,161 prepregnancy smokers, the majority (52.1 %) had stopped smoking at the first visit to antenatal care.

In order to estimate whether changes between pre-pregnancy and early pregnancy tobacco habits affect risk of preterm birth, we categorized tobacco habits into 5 groups: (1) non-tobacco users (non-users of snuff and cigarettes,

Table 1 Tobacco habits 3 months before pregnancy and in early pregnancy

| Pre-pregnancy | Early pregnancy | | | | | Total |
|------------------------|-----------------|------------|--------|------------------------|---------|---------|
| | Nonuser | Snuff user | Smoker | Snuff & cigarette user | Missing | |
| Nonuser | 607,430 | 1,049 | 729 | 9 | 4,941 | 614,158 |
| Snuff user | 11,983 | 8,321 | 70 | 16 | 187 | 20,577 |
| Smoker | 78,817 | 695 | 70,285 | 195 | 1,169 | 151,161 |
| Snuff & cigarette user | 1,378 | 563 | 279 | 481 | 17 | 2,718 |
| Missing | 33,545 | 33 | 4,875 | 2 | 44,353 | 82,808 |
| Total | 733,153 | 10,661 | 76,238 | 703 | 50,667 | 871,422 |

Nordic* women with live singleton births in Sweden, 1999–2009

* Women born in Denmark, Finland, Iceland, Norway, and Sweden

both before and in early pregnancy); (2) women who stopped using snuff (used snuff before but not in early pregnancy); (3) current snuff users (used snuff both before and in early pregnancy); (4) women who stopped smoking (smoked before but not in early pregnancy); and (5) current smokers (smoked both before and in early pregnancy). We excluded women who started to use tobacco in early pregnancy, women who changed between smoking and snuff use, and women who used both snuff and cigarettes ($n = 5,464$). The 5 studied groups included more than 99 % ($n = 776,836$) of women with available information about tobacco habits ($n = 782,300$).

Preterm birth was defined as a delivery before 37 weeks of gestation and was categorized into very (before 32 weeks) and moderately (32–36 weeks) preterm birth. Information on onset of labor is routinely recorded in a standardized manner by the midwife at the delivery ward, and is categorized into spontaneous onset of labor, vaginally induced onset of labor, and cesarean delivery before onset of labor. All births with a diagnosis of preterm pre-labor rupture of the membranes (PPROM, International Classification of Diseases, tenth version [ICD-10] code O42) were included as having a spontaneous onset of labor. We used this information to categorize preterm birth into spontaneous (spontaneous onset of labor and PPRM) and induced preterm birth (vaginally induced onset of labor and cesarean delivery before onset of labor).

Information on parity, body mass index (BMI), and whether the mother was living with the father-to-be was also collected at the first antenatal visit. Information about maternal age at delivery was collected when the woman was discharged from hospital. Information about mother's highest level of formal education was achieved by individual record linkage to the Education Registry (December 31st, 2010), using the person-unique Swedish National Registration Number. The Education Register was established in 1985 and includes information on the highest attained formal education, from elementary to postgraduate level [15]. The register is updated annually. The mothers' level of education was categorized as ≤ 12 or ≥ 13 years. The study was approved by one of the Regional Ethical Review Boards in Stockholm, Sweden.

Statistical analysis

First, we used univariable logistic regression analyses to estimate the associations between tobacco habits and risks of preterm birth. Using non-tobacco users as the reference group, we estimated risks of preterm birth among women who continued to use snuff, stopped using snuff, continued to smoke, or stopped smoking. We calculated crude odds ratios (ORs), presented with 95 % confidence intervals (CIs). In the univariable analyses, we used the entire sample

($n = 776,836$) when analyzing risks of very preterm birth (before 32 weeks) and preterm birth (before 37 weeks). In analysis of moderately preterm birth (32–36 weeks), we excluded very preterm births ($n = 4,271$). Second, we used multivariable logistic regression analyses to estimate ORs after adjustments for maternal age at delivery, early pregnancy BMI, parity, education, and whether the woman was living with the father-to-be. Observations with missing information on covariates were excluded in the multivariable analyses. The analyses of very preterm birth and all preterm birth were based on 695,722 observations, and the analyses of moderately preterm birth were based on 691,451 observations. All analyses were performed using the Statistical Analysis Software version 9.2 (SAS Institute, Inc., Cary, NC, USA). Because observations are not independent in women who delivered more than once during the study period, we calculated estimates using clustered data in the generalized estimation equation method (PROC GENMOD).

Results

In total, there were 4.8 % preterm births, of which 0.6 % were very preterm (before 32 weeks) and 4.2 % were moderately preterm births (32–36 weeks) (Table 2). Women who stopped using snuff or stopped smoking had similar rates of preterm birth as non-tobacco users. In contrast, current snuff users and smokers had higher rates of very and moderately preterm birth than non-tobacco users. High rates of preterm birth were also seen in the youngest and the oldest mothers, in primiparous women, in women who were obese ($\text{BMI} \geq 30$) in early pregnancy, in women who were not living with the father-to-be, and in women with ≤ 12 years of formal education.

The proportion of older women (≥ 35 years) was larger among current snuff users (22.5 %) than among women who stopped using snuff (16.0 %; Supplemental Table 1). Similarly, the proportion of older women (≥ 35 years) was larger among current smokers (17.3 %) than among women who stopped smoking (11.3 %). The proportion of primiparous women was lower among current snuff users and current smokers (and also among non-tobacco users) than among women who stopped using snuff or stopped smoking, respectively. The proportions of obese women, women not living with the father-to-be, and women with low (≤ 12 years) education were lower among women who stopped using snuff or stopped smoking than among current snuff users and current smokers, respectively.

Compared with non-tobacco users, women who stopped using snuff had similar crude odds ratios for preterm birth, both very and moderately preterm birth (Table 3). In the adjusted analyses, women who stopped using snuff before the first antenatal visit tended to have reduced risks of

Table 2 Rates of preterm (before 37 weeks), very (before 32 weeks) and moderately (32–36 weeks) preterm birth by maternal characteristics

| | Total number of births n | All preterm (n = 37,571) Rate % | Very preterm (n = 4,878) Rate % | Moderately preterm (n = 32,693) Rate % |
|---------------------------------|--------------------------------|---------------------------------------|---------------------------------------|--|
| Total | 776,836 | 4.8 | 0.6 | 4.2 |
| <i>Maternal characteristics</i> | | | | |
| Tobacco habits | | | | |
| Nonuser | 607,430 | 4.6 | 0.6 | 4.1 |
| Stopped using snuff | 11,983 | 4.6 | 0.5 | 4.1 |
| Current snuff user | 8,321 | 6.0 | 0.8 | 5.2 |
| Stopped smoking | 78,817 | 4.7 | 0.6 | 4.1 |
| Current smoker | 70,285 | 6.6 | 1.1 | 5.5 |
| Maternal age (years) | | | | |
| ≤19 | 12,778 | 6.5 | 1.1 | 5.4 |
| 20–24 | 91,038 | 5.4 | 0.7 | 4.8 |
| 25–29 | 239,490 | 4.9 | 0.6 | 4.3 |
| 30–34 | 280,653 | 4.4 | 0.6 | 3.9 |
| ≥35 | 151,402 | 4.9 | 0.7 | 4.2 |
| Missing | 1,475 | 7.0 | 1.0 | 6.0 |
| Parity | | | | |
| 1 | 352,761 | 6.0 | 0.8 | 5.2 |
| 2 | 285,046 | 3.6 | 0.4 | 3.2 |
| ≥3 | 139,029 | 4.4 | 0.6 | 3.8 |
| BMI | | | | |
| ≤19.9 | 67,535 | 5.2 | 0.6 | 4.6 |
| 20.0–24.9 | 391,311 | 4.5 | 0.6 | 3.9 |
| 25.0–29.9 | 178,009 | 4.8 | 0.6 | 4.2 |
| ≥30 | 79,566 | 5.9 | 0.9 | 5.0 |
| Missing | 60,415 | 5.2 | 0.7 | 4.6 |
| Living with the father-to-be | | | | |
| Yes | 728,973 | 4.8 | 0.6 | 4.2 |
| No | 38,432 | 6.1 | 0.9 | 5.2 |
| Missing | 9,431 | 5.5 | 0.8 | 4.7 |
| Education (years) | | | | |
| ≤12 | 380,220 | 5.3 | 0.7 | 4.6 |
| ≥13 | 380,802 | 4.3 | 0.5 | 3.8 |
| Missing | 15,814 | 6.5 | 1.1 | 5.4 |

Nordic women with live single births in Sweden, 1999–2009

preterm birth, although these risks did not reach statistical significance. Similarly, compared with non-tobacco users, women who stopped smoking had, after adjusting for confounders, a slightly reduced overall risk for preterm birth, and also reduced risks of very and moderately preterm birth. In contrast, women who continued to use snuff or to smoke had increased risks of preterm birth compared with non-tobacco users. If anything, these risks were higher for very than for moderately preterm birth. The adjusted analyses in Table 3 were performed after excluding observations with missing information on covariates. We therefore also calculated crude odds ratios for the subpopulation with complete information on covariates. However, in analyses of very (<32 weeks), moderate

(32–36 weeks) and all preterm births (≤36 weeks), there were only minor differences in crude odds ratios between the total population and the population with complete information on covariates (data not shown).

As we wanted to investigate if change of exposure (from being exposed to being unexposed to snuff or cigarettes) was associated with reduced risks of preterm birth, we also compared risks between those who quit versus those who continued to use snuff or smoke, respectively. Compared with snuff users in early pregnancy, women who stopped using snuff had a reduced risk of preterm birth (adjusted OR = 0.71, 95 % CI 0.63–0.81), and the protective effect of stopping using snuff appeared to be larger for very than for moderately preterm birth (adjusted ORs = 0.61, 95 %

CI 0.43–0.87; and 0.73, 95 % CI 0.64–0.85, respectively). Similarly, with smokers in early pregnancy as a reference, women who stopped smoking had a reduced risk for preterm birth (adjusted OR = 0.69, 95 % CI 0.66–0.73), and the reduction in risk was more pronounced for very than for moderately preterm births (adjusted ORs = 0.54, 95 % CI 0.48–0.62; and 0.73, 95 % CI 0.69–0.76, respectively).

Of all preterm births, 70 % had a spontaneous onset of labor, 27 % had an induced onset, and in 3 % onset of labor was unknown (Table 4). Compared with non-tobacco users, women who stopped using snuff tended to have decreased risks of both spontaneous and induced preterm births, and among women who stopped smoking these risks were significantly reduced. Compared with non-tobacco users, current smokers and current snuff users had increased risks of preterm birth with spontaneous and

induced onset of labor. If anything, these associations were stronger for spontaneous than induced preterm birth.

Discussion

In this nation-wide Swedish study, we found that women who stopped using snuff or stopped smoking reduced their risks of very and moderately preterm birth, and that the reduction in risks applied to both spontaneous and induced preterm births. In contrast, continued snuff use and smoking were associated with increased risks of preterm birth. We also found that more than 50 % of all women who used snuff or smoked 3 months before pregnancy had given up the habit at their first visit to antenatal care.

Table 3 Crude and adjusted odds ratios for preterm by change of tobacco habits in early pregnancy

| | Crude odds ratio | 95 % CI | Adjusted ^b odds ratio | 95 % CI |
|---|------------------|-------------|----------------------------------|-------------|
| Preterm (before 37 weeks) (n = 33,172) | | | | |
| Nonuser ^a | 1.00 | | 1.00 | |
| Stopped using snuff | 1.01 | (0.92–1.10) | 0.92 | (0.84–1.01) |
| Current snuff user | 1.34 | (1.22–1.48) | 1.29 | (1.17–1.43) |
| Stopped smoking | 1.02 | (0.99–1.06) | 0.90 | (0.87–0.94) |
| Current smoker | 1.43 | (1.38–1.48) | 1.30 | (1.25–1.36) |
| Very preterm (before 32 weeks) (n = 4,271) | | | | |
| Nonuser ^a | 1.00 | | 1.00 | |
| Stopped using snuff | 0.97 | (0.75–1.25) | 0.88 | (0.68–1.14) |
| Current snuff user | 1.50 | (1.17–1.93) | 1.44 | (1.12–1.86) |
| Stopped smoking | 1.04 | (0.94–1.15) | 0.91 | (0.82–1.01) |
| Current smoker | 1.84 | (1.69–2.00) | 1.68 | (1.52–1.84) |
| Moderately preterm (32–36 weeks) (n = 28,901) | | | | |
| Nonuser ^a | 1.00 | | 1.00 | |
| Stopped using snuff | 1.01 | (0.92–1.11) | 0.93 | (0.84–1.02) |
| Current snuff user | 1.32 | (1.19–1.46) | 1.27 | (1.15–1.41) |
| Stopped smoking | 1.02 | (0.98–1.06) | 0.90 | (0.86–0.94) |
| Current smoker | 1.37 | (1.32–1.41) | 1.25 | (1.20–1.30) |

^a Reference group

^b Odds ratios were adjusted for early pregnancy body mass index, maternal age, parity, education, and cohabitation. *CI* confidence interval

Table 4 Rates and adjusted odds ratios for spontaneous and induced onset of preterm birth (before 37 weeks) by change of tobacco habits in early pregnancy

| | Spontaneous preterm birth (n = 23,300) | | | Induced preterm birth (n = 9,051) | | |
|----------------------|--|-------------------------|-------------|-----------------------------------|-------------|-------------|
| | Rate | Odds ratio ^b | 95 % CI | Rate | Odds ratio* | 95 % CI |
| Nonuser ^a | 3.2 | 1.00 | | 1.3 | 1.00 | |
| Stopped using snuff | 3.3 | 0.92 | (0.83–1.02) | 1.2 | 0.93 | (0.78–1.10) |
| Current snuff user | 4.2 | 1.30 | (1.15–1.45) | 1.7 | 1.27 | (1.07–1.52) |
| Stopped smoking | 3.4 | 0.92 | (0.88–0.96) | 1.2 | 0.86 | (0.79–0.92) |
| Current smoker | 4.5 | 1.32 | (1.26–1.38) | 1.7 | 1.20 | (1.12–1.29) |

^a Reference group

^b Odds ratios were adjusted for early pregnancy body mass index, maternal age, parity, education, and cohabitation
CI confidence interval

Both snuff use and smoking have previously been associated with risk of preterm birth [4, 16, 17]. If snuff use and/or smoking are in the causal pathway, a change from being exposed to being unexposed should lead to a reduced risk of preterm birth. Studies from other countries have shown that women who stop smoking in early pregnancy reduce their risk of preterm birth to a similar level to that of non-smokers [8, 9, 18]. We have previously reported that women who quit smoking from first to second pregnancy, reduce their risk of preterm birth in the second pregnancy [19]. These findings favor the hypothesis that maternal smoking causes a direct toxic exposure during pregnancy which increases the risk of preterm birth. In the present investigation, women who stopped using snuff before the first antenatal visit reduced their risk of preterm birth. In contrast, both women who continued to use snuff or continued to smoke had increased risks of preterm birth. Among both snuff users and smokers, stronger effects were seen for very than for moderately preterm birth, and risks were possibly also higher for spontaneous than induced preterm birth.

As far as we know, no previous study has shown that stop using snuff (or other kinds of smokeless tobacco) in early pregnancy confers a protective effect on risk of preterm birth. In contrast to smoking, which, in addition to nicotine, also contains a large number of combustion products, Swedish snuff essentially only includes nicotine. Our findings indicate that nicotine plays an important role in the mechanisms by which snuff use and smoking during pregnancy increases the risk of preterm birth [20].

The mechanism by which nicotine may influence risk of preterm birth is not clear [4, 21]. Infection and/or inflammation are causally associated with risk of preterm birth, and the underlying molecular pathophysiology has also been described [22]. Smoking seems to influence all aspects of the immune system [21, 23, 24], and if this is due to nicotine [25], it could, at least partly, explain the increased risk of spontaneous preterm birth among tobacco users. Induced preterm births are caused by fetal or maternal indications, such as fetal growth restriction and maternal complications. Cigarette smoking increases risks of fetal growth restriction and several maternal complications [1, 8–10]. However, one earlier report shows that the smoking-related risk of preterm birth remained essentially unchanged after exclusion of pregnancies with other smoking-associated complications [25]. Further, snuff use during pregnancy has not been shown to have a strong association with fetal growth or with pregnancy complications associated with induced preterm birth [20]. Thus, the mechanism by which nicotine increases risk of preterm birth remains largely unexplained.

We unexpectedly found a lower risk of preterm birth among women who stopped smoking than among women

who did not use tobacco, neither before nor during pregnancy. For women who stopped using snuff, we obtained a similar risk reduction, although with less precision. Preterm birth is associated with abnormal placentation with a suboptimal placental invasion of trophoblast cells deep into the deciduas to the spiral arteries [26]. More than 50 % of women who were snuff users or smokers 3 months before pregnancy had given up the habit at registration to antenatal care (usually at the 8th to 12th gestational week). We do not know the exact time when women quit smoking or using snuff. However, most women who stop using snuff or stop smoking during pregnancy do so very early in pregnancy, while learning that they are pregnant [1]. One speculative hypothesis to explain the lower risk of preterm birth among women who stopped smoking or using snuff is that very early exposure to nicotine during pregnancy may be beneficial: nicotine exposure may enhance placentation, since early placental development occurs in a predominantly low oxygen environment and nicotine reduces the uterine blood flow [27–29]. However, at the end of first trimester, intervillous blood flow should increase for appropriate trophoblast differentiation into an invasive phenotype [30]. Therefore, extended nicotine exposure, with a decreased uterine blood flow after first trimester, would be expected to have a negative long-term effect, which also is in agreement with the findings of this study. Another possibility for this unexpected finding might be a generally more healthy life style among women who decided to and succeeded to stop using snuff or to stop smoking compared with non-tobacco users. The percentages of primiparous were larger among women who stopped using snuff or stopped smoking than among non-tobacco users. Women who are expecting their first child may be more health-conscious also in other aspects. Thus, the slightly lower risk of preterm birth among smoking and snuff quitters vs. non-tobacco users may be due to residual confounding [31].

Like snuff, nicotine replacement therapy (NRT) mainly contains nicotine. NRT usually generates lower nicotine levels than smoking and probably also snuff, but nicotine level remains continuously high during use [32]. There is insufficient evidence for the NRT's safety during pregnancy [32–35]. The smoking and snuff-related risks of preterm birth in our study indicate that nicotine is likely to play an important role in the etiology of preterm birth. Thus, NRT is probably not a safe alternative to smoking during pregnancy.

Major strengths of this study include the population-based design, with information on snuff use and smoking both before and in early pregnancy. In this nation-wide cohort of more than 700,000 women, information on snuff and smoking habits was collected in early pregnancy, which precludes recall bias. We adjusted for maternal

characteristics, such as maternal age, parity, BMI, and social factors. The major weakness of this study is that information on tobacco was based on interviews performed by the midwife at first visit to antenatal care. We had no access to biological samples, including cotinine measurements to validate this information. Most women in Sweden are aware of potential adverse effect of tobacco on pregnancy outcomes, and underreporting of tobacco use must be considered. Self-reported information on maternal snuff use has not been validated, but the validity of self-reported smoking during pregnancy is acceptable in Sweden [36].

In conclusion, women who stop using snuff or stop smoking in early in pregnancy reduce their risk of preterm birth. The similarities in risks, between persistent snuff users and smokers, and between women who quit using snuff or quit smoking, suggest that antenatal exposure to nicotine is involved in the mechanisms by which maternal use of tobacco increases the risk of preterm birth.

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