An update on prevalence and risk of snus and nicotine replacement therapy during pregnancy and breastfeeding

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Abstract

Aims

In parallel with falling smoking rates, use of the oral moist tobacco product snus increases among women in reproductive age. We report an update on prevalence and effects of maternal use of snus and nicotine replacement therapy (NRT) during pregnancy and breastfeeding.

Methods

A literature search of human studies in Medline, PubMed and EMBASE was conducted from September 2016 to May 2018, with stepwise screening of abstracts and subsequent relevant full text papers for inclusion in Scandinavian and English languages.

Results

Based on three studies, the prevalence of snus use in pregnancy was up to 3.4% in the first trimester and 2.1% in the third trimester. In 12 studies we found increased risk of several adverse effects, especially preterm delivery, stillbirth and small for gestational age associated with maternal snus use during pregnancy. Knowledge on effects of NRT during pregnancy was conflicting and inconclusive in 10 studies. We did not identify any studies on prevalence or potential health effects of snus or NRT during breastfeeding.

Conclusion

Few studies with updated data on the prevalence and adverse health effects of maternal use of snus and NRT during pregnancy were found. No studies during breastfeeding were identified.

Key Notes:

- As young women increasingly use the oral moist tobacco product snus and nicotine replacement therapy (NRT), this study provides an update on the prevalence and effects during pregnancy and breastfeeding.
- The prevalence of snus during pregnancy was low with increased risk of preterm delivery, stillbirth and small for gestational age, while prevalence of NRT was lacking and effects conflicting.
- Studies on prevalence and effects during breastfeeding were not found.

Key words: breastfeeding, infancy, nicotine exposure, pregnancy, snus.

INTRODUCTION

It is well known that maternal cigarette smoking during pregnancy increases the risk of adverse health effects in the unborn child (1). In the past decades smoking rates has declined among women in reproductive age (1). The same trend has been seen during pregnancy with a nearly 50% reduction observed from 2005 to 2015 in Norway and Sweden based upon national statistics.

In parallel with the falling smoking rates, there has been a shift towards the use of other products containing nicotine. A rapid increase in the use of electronic cigarettes has been observed in countries such as the USA (2), while the use of other smokeless tobacco products such as snuff, chewing tobacco and dip do not seem to follow the same trend (2). In contrast to several countries, sales of electronic cigarettes is currently banned in Norway and Sweden, with limited use among young women at present. Rather, an increasing use of the Swedish moist tobacco product called snus which is placed under the upper lip, has been observed (3). Additionally, nicotine from smoking cessation aids such as nicotine replacement therapy (NRT), is one of the five most sold pharmaceutical substances without prescriptions in Norwegian pharmacies and grocery stores. In 2017, the use of snus in the general population exceeded that of smoking, with daily use of snus reported by 13% of women aged 16-34 years according to Norwegian national statistics.

Smoking is one of the most important modifiable risk factors during pregnancy, increasing the risk of premature delivery, low birth weight, a variety of birth defects, sudden infant death syndrome, stillbirth as well as perinatal mortality (1). Noteworthy, both human and animal studies provide evidence that several of the *in utero* effects

of smoking seen in the offspring are mediated by nicotine (1). Studies have demonstrated that nicotine exposure *in utero* leads to adverse structural and functional changes in the brain and behavioural changes, as well as inhibition of lung development, lung function in the offspring and respiratory health later in life (4). In addition, maternal smoking during pregnancy may have a persistent effect on offspring cardiovascular health (4). Tobacco smoking during breastfeeding increase the risk of offspring neurobehavioral disorders and sleep disruption (4). There has been shown a relationship between sudden infant death disorder and neonatal tobacco exposure (4). Despite the contents of nicotine, which is highly addictive, in both snus and NRT, they have been considered safer, alternative products to combustible tobacco.

Nicotine from cigarettes readily, and especially under alkaline conditions, crosses mucosal membranes in the airways and mouth and reaches the systemic circulation (5). Whereas nicotine uptake from snus in the mouth is slower than from cigarettes, the blood concentration of nicotine reaches similar levels, remains higher over time and show a slower decline, leading to a greater total systemic dose of nicotine (5). The amount of nicotine varies between different NRT products such as transdermal patches, chewing gum and lozenges, but generally give lower nicotine concentrations than that from smoking and snus (5). Nicotine is metabolised mainly by the liver to less active metabolites, i.e. cotinine, which subsequently are excreted primarily by the kidneys (5).

Nicotine is a potent stimulant acting as an agonist on most nicotinic acetylcholine receptors, except at some receptor subunits where it has antagonistic effects.

Besides the central and peripheral nervous system, these receptors are present in organs and tissues such as muscle, lung, endothelium, kidneys, and skin, though the development of the brain and lung is thought to be particularly vulnerable to nicotine *in utero* (1).

Nicotine easily passes the placenta and can be detected in human fetal circulation and amniotic fluid at concentrations higher than those in the maternal plasma (1). Further, compared with smoking, snus used by breastfeeding women has been shown to give higher levels and prolonged presence of nicotine in breast milk, with at least 12.5 hours in snus users and four hours in smokers following abstinence (6).

As exposure to nicotine products during fetal life and infancy may confer health-related risks, it is essential to identify the extent of nicotine exposure from these. The primary aim of the present study was to identify the prevalence of maternal use of snus and NRT during pregnancy and breastfeeding and secondary to provide an updated overview of knowledge on the effects of such use.

METHODS

We conducted semi structured literature searches to identify original human studies investigating prevalence and adverse offspring health effects of snus and NRT exposure during pregnancy and breastfeeding period. The search was conducted between September 2016 and May 2018 in Medline, PubMed and EMBASE. We included studies published from 2008 to most recent in English and Scandinavian languages. The following search terms were used: pregnancy, lactation, breastfeeding, nicotine, nicotine replacement therapy, snus, snuff, smokeless tobacco, smokeless, tobacco, prevalence, adverse effects, effects, outcome, infant, fetus, offspring in various combinations using the Boolean AND and OR. We also identified papers from reference lists in relevant articles. Three authors (IK, LSN, KESB) conducted the data screening and extraction. First, we individually browsed through headlines and abstracts of the 392 articles retrieved during the initial search in 2016. Secondly, we excluded papers based upon animal studies, duplicates, non-available full-text articles and articles that did not include relevant information. Regular update searchers were performed until May 2018. Based on the final full text assessments we decided which papers to be included.

RESULTS

Overall 25 studies were included after the stepwise assessment of the results from the literature searches. Only three studies regarding prevalence of snus use during pregnancy were found, and 12 studies on the effects during pregnancy. We found 10 studies on the effects of NRT during pregnancy. No studies were found on prevalence or effects of snus or NRT during breastfeeding.

Prevalence of snus

The three studies reporting the prevalence of snus use in or after pregnancy included one population-based cohort from Sweden, one from the USA and one register study from Norway (7-9) (Table 1). Data were obtained from national birth register (7), a survey (9), and electronic birth records (8) based on self-reports by the study subjects. The number of respondents ranged from 388 to 1,371,274. None of the studies had verification of snus use by biomarkers such as nicotine or cotinine levels in plasma, hair or urine.

Overall, the use of snus in pregnancy reported in the three countries with available data, was less than 1% in the USA, 1.1% in Sweden and 3.4% in Norway (7-9). Among the 388 pregnant women included in the American Population Assessment of Tobacco and Health study, less than 1% reported use of snus, while 4.6% of the smoking pregnant women also used snus.

In a population based electronic birth registry study of 10,583 births in Norway, use of maternal snus in pregnancy doubled in the three years from 2012 to 2014, from 1.7% to 3.4% during the first trimester, with the corresponding increase from 1.2% to 2.1% in the last trimester (8). The increase was most pronounced among the youngest

women aged 16-24 years with 4.6% using snus in the last trimester. Snus use prior to pregnancy increased in the same period from 3.6% in 2012 to 6.8% in 2014, with significantly more women quitting snus compared to cigarette smoking during the first trimester (57.5% versus 45.2%) and the third trimester (71.4% versus 58%). Data for the birth registry were recorded by midwives at the routine antenatal visit at 18 weeks of gestation for information of daily or sometimes use of snus prior to and in the first trimester, and at the delivery ward at birth for the last trimester.

The largest study reported data from 1,371,274 singleton births in the Swedish Medical Birth Register collected from 1999 to 2012. Midwives recorded any use of snus three months prior to pregnancy and up to the first antenatal visit at 8-12 weeks of gestation. Although 2.2% reported snus use three months before pregnancy, 60% had stopped before the antenatal visit, while 1.1% used snus in early pregnancy. Snus was most frequently used among Swedish women aged 25-34 years (7). In addition, updated data from the National Board of Health and Welfare in Sweden, showed maternal snus use of 1.2% in early pregnancy and 0.7% in late pregnancy in 2016. Similar statistics were not available from Norway.

We did not identify any studies on the prevalence of snus use during breastfeeding.

Prevalence of NRT

We found no prevalence data on the use of NRT during pregnancy or breastfeeding period.

Adverse effects of snus

Adverse effects of snus use in pregnancy were observed in several human studies, as outlined in Table 2, with effects of smoking and snus during pregnancy reported in 10 cohort studies (7, 10-17) and in one study based upon sibling analysis (18). Furthermore, one case report describing neonatal withdrawal symptoms after exposure to around 20 doses of snus per day during pregnancy was identified (19).

The population-based cohorts from Sweden used information collected from 1999 to 2006-2010 in the Swedish Medical Birth Register of 605,023 to 1,371,274 women; recording snus use 3 months before pregnancy and present use at the first antenatal care visit around 12-15 weeks of gestation. In these studies use of snus in pregnancy increased risk of preterm birth, especially before 32 weeks (7, 10, 16), small for gestational age births (11) and stillbirth (12, 20). Common confounding factors were maternal age at delivery, early pregnancy body mass index, parity, education, co-habitation by mother and father, pre-gestational diabetes and essential hypertension. In a sibling analyses using a subgroup from the Swedish Medical Birth Register, Juarez and Merlo (18) reported minor, though not significant effects on birth weight reduction with the use of snus during pregnancy. Other studies indicate a possible link between snus use in pregnancy and preeclampsia (17), increased risk of neonatal apnoea (13) and oral cleft malformation (14). A prospective observational study reported altered heart rate variability in the 23 infants exposed to maternal snus use similar to that found in the 13 exposed to cigarettes in pregnancy, as compared with the 19 controls. The nicotine dose was estimated four times pre- and postnatally based on questionnaires collecting detailed information about frequency of use and type of product. The infants' urine cotinine concentration was measured at 4-10 weeks after delivery. All infant controls had cotinine levels <0.7 ng/mL, snus

group ranged from 0-408 ng/mL and the cigarette smoking group from 0-129 ng/mL. In this study it was apparent that tobacco, regardless of form, timing and type of exposure, could affect the developing infant (15).

We did not identify any studies concerning snus use during breastfeeding and health effects on the offspring.

Adverse effects of NRT

In our search of effects on the offspring by use of NRT in pregnancy 10 original papers were identified (21-30) as outlined in Table 3**.** Four papers reported results from two randomised controlled trials primarily assessing the effects of smoking cessation during pregnancy by use of NRT patches compared to placebo patches, in pregnant women smoking at least five cigarettes a day. In the French Study of Nicotine Patch in Pregnancy trial including 402 pregnant women from 2007-2013, no significant impact on smoking cessation was found with only 5% in both groups completely abstaining from smoking. Nor did they observe significant impact on offspring birth weight by mothers randomised to NRT patches compared to placebo (21). Similarly, in the UK-based Smoking, Nicotine And Pregnancy trial conducted from 2007-2012 (22), no significant improvements in terms of abstinence from smoking or risk of adverse pregnancy or birth outcomes were found by adding a nicotine patch or matched placebo to behavioural cessation among the 1,050 pregnant women who were included. However, the compliance of smoking cessation was low and non-significant between the NRT and placebo group (9.4% versus 7.6%, respectively), which limited the assessment of safety in this study. On the other hand, the authors reported that the children at two-year of age born to women who used

NRT were more likely to have survived without any developmental impairment compared to the placebo group (23, 24).

Effects associated with use of NRT patches or gum were reported from three population-based cohorts from UK, USA and Denmark resulting in several papers with data collected in different time periods between 1996-2012 and including from 5716 to 220,630 subjects (25-30). Information was obtained from national birth registers, primary care records, birth certificates, self-administrated questionnaires and computer-assisted telephone interviews. The birth register studies from Denmark (28) and the USA (27) concluded that maternal use of NRT could increase the risk of a low birth weight. There was no evidence of increased risk of stillbirths in the Danish Medical Birth Register (1996-2002) (30) or the UK based primary care pregnancy register (26) when comparing the use of NRT patches to non-smoking pregnant women. Dhalwani et al observed an increased risk of respiratory anomalies associated with use of NRT in pregnancy from a pregnancy cohort study using prospective data from primary care records (25). The birth cohort study from Denmark also found that infants exposed to NRT prenatally had an increased risk of infantile colic comparable to those exposed to tobacco smoke (29).
We did not identify any studies concerning the use of NRT during breastfeeding and, or potential health effects.

DISCUSSION

Recent studies report maternal use of snus during pregnancy in 3.4% of women in the first trimester in pregnancy in Norway (8), 1.1% in Sweden (7) and less than 1% in the United States (9), while we found no information on the use during

breastfeeding. The differences in prevalence probably reflect data collection from the different time periods 1999-2012 versus 2012-2014, with higher prevalence in the latter period. This corresponds well with the increasing use of snus among Swedish and Norwegian young women in recent years. The lower rate of snus use in the USA compared to Norway and Sweden may be explained by differences in availability as well as frequency of use other nicotine products such as electronic cigarettes (2). We did not identify any studies on prevalence of use of NRT during pregnancy and breastfeeding. Prescription rates of NRT during and after pregnancy are available, but as NRT is often purchased without prescription, these rates may not be representative for the total prevalence.

Most human studies assessing effects on the offspring were based on data from large, population-based registers with limited details on the levels of nicotine exposure. To comparison there has been conducted several animal studies which have shown detrimental effects on the offspring especially in lung and brain development (1). These studies indicate that many of the adverse effects of maternal smoking are mediated by nicotine, suggesting that the use of products containing nicotine such as snus, NRT and electronic cigarettes are not safer than combustible tobacco for the unborn child. There is an urgent need for large, well-designed human studies to identify potential risk for the unborn and newborn child of non-smoking nicotine exposure *in utero*.

The risk of adverse health effects on the offspring exposed to NRT in pregnancy appeared conflicting and inconclusive. One explanation may be the varying level of nicotine exposure in the different studies. Register studies on NRT in pregnancy

showed increased risk of low birth weight and preterm birth (27) as well as infantile colic (29), while randomised controlled trials did not show increased risk of adverse pregnancy and birth outcomes (22-24). The efficacy of NRT on smoking cessation was questioned by one of the studies (23). Hence, the safety, as well as the efficacy, of NRT during pregnancy is unclear.

There are several adverse health effects on the offspring associated with the exposure to cigarette smoking during breastfeeding (4). We found no study assessing potential effects on the infant by snus and NRT exposure through breast milk. A recent study reported however that snus users had higher levels of nicotine in their breast milk compared with smokers (6). Breastfeeding is important for infant health, yet potential risk of exposure to nicotine from breast milk remains unknown. Studies into prevalence of snus or NRT use in pregnancy and by breastfeeding mothers, as well as potential effects in their infants are urgently needed to provide well documented and balanced advice to young women on the risks of tobacco and products containing nicotine.

Limitations of this mini review are that there are few prospective studies and in general limited detailed knowledge on the level of nicotine exposure from snus linked to adverse effects. In addition we lack updated knowledge since many of the results are based on data gathered more than one decade ago.

CONCLUSION

Changing patterns of nicotine use among young females, including during pregnancy, might reflect a public notion that snus and NRT may be relatively safely

used in pregnancy. Results from our literature searches do not support this assumption. However, adverse effects of snus and NRT have been shown to negatively impact pregnancy outcomes, particularly in large population-based registry data. Little is known about adverse health effects in infants exposed to snus use by breastfeeding women. While health policies aim at reducing smoking exposure to the unborn child or infant, other ways to consume nicotine should also be strongly discouraged, as they do not appear safe for the health of the offspring.

Abbreviations: NRT: Nicotine replacement therapy

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Table 1 Prevalence of snus during pregnancy

Authors(s), year, reference	Prevalence	Country Year	Number	Design
Dahlin et al. 2016 (7)	1.1% in pregnancy	Sweden 1999-2012	1,371,274	Population-based cohort The Swedish Medical Birth Register
Rygh et al. 2016 (8)	3.4% first trimester, 2.1% third trimester	Norway 2012-2014	10,583	Data from electronic birth record
Kurti et al. 2017 (9)	<1% in pregnancy	United States 2013-2014	388	Longitudinal cohort The Population Assessment of Tobacco and Health Study survey

Table 2: **Adverse effects of snus during pregnancy**

Authors(s), year, reference	Adverse effects Snus	Country Year	Number	Design
Baba et al. 2012 (10)	Increased risk preterm birth (OR 1.29, 95% CI 1.17-1.43)	Sweden 1999-2009	776,836	Population-based study The Swedish Medical Birth Register
Baba et al. 2013 (11)	Increased risk for small for gestational age births (OR 1.26, 95% CI 1.09-1.46)	Sweden 1999-2010	846,411	Population-based cohort The Swedish Medical Birth Register
Baba et al. 2014 (12)	Increased risk stillbirth (OR 1.43, 95% CI 1.02-1.59), but not early neonatal mortality	Sweden 1999-2010	851,371	Population-based cohort The Swedish Medical Birth Register
Dahlin et al. 2016 (7)	Associated with risk of medically indicated extremely preterm birth (OR 1.58, 95% CI 1.14-2.21)	Sweden 1999-2012	1,371,274	Population-based cohort The Swedish Medical Birth Register
Gunnerbeck et al. 2011 (13)	Increased risk of neonatal apnoea (OR 1.96, 95% CI 1.30-2.96)	Sweden 1999-2006	609,551	Population-based cohort The Swedish Medical Birth Register
Gunnerbeck et al. 2014 (14)	Associated with increased risk oral cleft malformation (OR 1.48, 95% CI 1.00-2.21)	Sweden 1999-2009	969,758	Population-based cohort The Swedish Medical Birth Register
Juarez and Merlo 2013 (18)	Minor (not significant) effect on birth weight reduction	Sweden 2001-2010	8,861	Sibling analysis The Swedish Medical Birth Register
Nordenstam et al. 2017 (15)	Altered Heart Rate Variability in infant	Sweden	56	Prospective, observational study
Wikstrom et al. 2010 (20)	Increased risk stillbirth	Sweden 1999-2006	610,879	Population-based cohort The Swedish Medical Birth Register
Wikstrom et al. 2010 (17)	Slightly higher risk of preeclampsia	Sweden 1999-2006	605,023	Population-based cohort The Swedish Medical Birth Register
Wikstrom et al. 2010 (16)	Increased risk of very and moderately preterm birth with both spontaneous and induced onsets	Sweden 1999-2006	610,199	Population-based cohort The Swedish Medical Birth Register
Froisland 2017 (19)	Nicotine withdrawal syndrome in a newborn	Norway 2017		Case report

Table 3: **Adverse effects of NRT during pregnancy**

Authors(s), year, reference	Adverse effects NRT	Country Year	Number	Design
Berlin et al. 2014 (21)	NRT patch did not increase smoking cessation rates or birth weights despite adjustment of nicotine dose to match levels attained when smoking, and higher than usual doses	France 2007-2013	402	Randomised controlled trial The Study of Nicotine Patch in Pregnancy trial
Coleman et al. 2012 (22)	NRT patch combined with behavioural cessation support did not significantly increase the rate of abstinence from smoking until delivery or the risk of adverse pregnancy or birth outcomes	England 2007-2010	1,050	Randomised controlled trial The Smoking and Nicotine in Pregnancy trial
Cooper et al. 2014 (23)	NRT patches had no significant effect on smoking in pregnancy; however, 2-y-olds born to women who used NRT more likely survived without developmental impairment	England 2007-2010	1,050	Randomised controlled trial The Smoking and Nicotine in Pregnancy trial
Cooper et al. 2014 (24)	NRT compared to placebo more likely to have infants with unimpaired development. NRT had no effect on prolonged abstinence from smoking but did cause a temporary doubling of smoking cessation shortly after randomisation, which could explain findings	England 2007-2010	888	Randomised controlled trial The Smoking and Nicotine in Pregnancy trial
Dhalwani et al. 2015 (25)	No significantly increased risk for most system-specific major congenital anomalies except for respiratory with maternal NRT prescribed during pregnancy	United Kingdom 2001-2012	192,498	Longitudinal, prospective pregnancy cohort The Health Improvement Network database of electronic primary care records
Dhalwani et al. 2018 (26)	No significant association between prescribed NRT during pregnancy and odds of stillbirth compared with non-smoking women	United Kingdom 2001-2012	220,630	Longitudinal, cross-sectional cohort The Health Improvement Network database of electronic primary care records
Gaither et al. 2009 (27)	Increased risk of low birth weight and preterm birth when prescribed/recommended NRT	USA 2004	5,716	Population-based surveillance system. The 2004 Phase V Pregnancy Risk Assessment Monitoring Systems, self-administered questionnaires and data from birth certificates
Lassen et al. 2010 (28)	Possible negative effect on birth weight	Denmark 1996-2002	72,761	Population-based The Danish National Birth Cohort, computer-assisted telephone interview
Milidou et al. 2012 (29)	Prenatal exposure to NRT increased risk of infantile colic comparable to those exposed to tobacco smoke	Denmark 1996-2002	63,128	Population-based The Danish National Birth Cohort, computer-assisted telephone interview
Strandberg-Larsen et al. 2008 (30)	No increased risk of stillbirth	Denmark 1996-2002	5,716	Population-based The Danish National Birth Cohort, computer-assisted telephone interview