Int J Public Health (2014) 59:599–608
DOI 10.1007/s00038-014-0558-6

REVIEW

# Smokeless tobacco use in pregnancy: an integrative review of the literature

**Angela Ratsch · Fiona Bogossian**

Received: 14 October 2013 / Revised: 14 April 2014 / Accepted: 16 April 2014 / Published online: 4 May 2014


**Abstract**
*Objectives* To systematically critique and summarise the available evidence on the outcomes of smokeless tobacco use in pregnancy to inform the public health response.
*Methods* In March 2013, a search was conducted of observational studies where the exposure to smokeless tobacco during pregnancy and maternal, placental and/or neonatal outcomes was assessed. Two reviewers extracted data and completed quality assessment of the literature utilizing the Agency for Healthcare Research and Quality criteria (West et al. 2002).
*Results* The search resulted in 211 articles, 21 (10 %) of which met the final criteria for integrative review. Ten (10) of the studies are from India, seven (7) from Sweden, two (2) from Alaska and one (1) each from South Africa and Pakistan.
*Conclusions* Many studies lacked sufficient power to estimate precise risks. Most reports were hindered by imprecise measures of exposure and lack of confounding variable control. However, there were indications that maternal smokeless tobacco use increases rates of stillbirth, low birth weight and alters the male:female live birth ratio. Maternal smokeless tobacco use may not be safe for mother or foetus.

**Keywords** Smokeless tobacco · Pregnancy · Maternal outcomes · Perinatal outcomes

## Introduction

Nicotinic acetylcholine receptors (nAChRs) are ionotropic receptors located in the central and peripheral nervous system and are ordinarily triggered by endogenous acetylcholine (ACh), however, nAChR's are also triggered in the presence of nicotine (Benowitz et al. 2009). Critically, nicotine crosses the placental barrier effecting nAChRs in the developing foetus (Lambers and Clark 1996). Foetal nAChRs emerge and begin to form connections during the second trimester, with axonal construction and synaptic connections continuing after birth and into childhood (Slotkin 1997). Nicotine exposure in-utero impacts tissues and organs with nAChRs and results in accelerated cell development relative to tissue and organ age, i.e. there are fewer cells appropriate to their stage and age (Lambers and Clark 1996). Significantly, there is a deficit in the number of neurons in the brain, synaptic level damage to the respiratory center in the medulla oblongata, and, equivalent damage to the adrenal glands resulting in an absence of adrenaline release during hypoxia (Law et al. 2003; Slotkin et al. 1995). Research demonstrates that these foetal neuroteratogenic effects of nicotine occur at an exposure/dose threshold level below that which causes Intrauterine Growth Retardation (IUGR) (Slotkin et al. 1997).

While IUGR is frequently recognized as a major defining effect of foetal exposure to maternal smoking (Aagaard-Tillery et al. 2008), other significant outcomes include pre-term birth, stillbirth, and placenta previa and abruption. The adverse placental and foetal pathologies primarily responsible for these outcomes are attributed to a

**Electronic supplementary material** The online version of this article (doi:10.1007/s00038-014-0558-6) contains supplementary material, which is available to authorized users.

A. Ratsch (✉)
Queensland Health and School of Nursing and Midwifery, The University of Queensland, Brisbane, Australia
e-mail: angela.ratsch@health.qld.gov.au

F. Bogossian
School of Nursing and Midwifery, The University of Queensland, Brisbane, Australia

complex matrix of events extensively explored in other works (see Ginzel et al. 2007). These pathologies effectively decrease foetal cell oxygenation and ultimately reduce anthropometric measurements in terms of foetal growth, weight and fat mass (Jauniaux and Burton 2007; Reeves and Bernstein 2008; Rogers 2009). The contribution of nicotine per se to these outcomes is the subject of ongoing animal studies (Khalki et al. 2012; Bruin et al. 2010).

### Tobacco, nicotine and pH

Absorption of nicotine is pH dependant. The combusted nicotine in cigarettes has a pH 5.5–6.0 whilst the oral pH is 6.2–7.4, thus there is little oral absorption of nicotine from smoking, but once in the respiratory tract, the nicotine is rapidly absorbed in the lung—pH 7.4 (Richter and Spierto 2003). Cigar and pipe tobacco have a higher alkalinity smoke (≥pH 6.5) enabling significant oral absorption (Caldwell et al. 2012; Richter and Spierto 2003). Snuff and chewing tobacco (smokeless tobacco) are often buffered commercially or by users with alkaline modifiers to facilitate absorption across the oral mucosa. Benowitz et al. (1988) demonstrated that smokeless tobacco blood nicotine concentrations reach a high plateau level which persists for 2 h or more after exposure has ceased.

### Smokeless tobacco (ST)

This paper refers to smokeless tobacco as non-burning tobacco administered through the oro-nasal compartments including ingestion of tobacco leaves and rubbing tobacco pastes/powders on the gums and oral mucosal surfaces. Formulations include commercial and non-commercial products including those with flavourings and/or alkaline modifiers. England et al. (2010) document an extensive list of ST products that may be categorised and described as follows:

1. Moist snuff: finely ground or shredded tobacco, a 'dip' of which is held in the mouth between the cheek and gum/tongue. The product is loose-leaf or commercially available in small paper or cloth packets. Regional terms include khaini, snus, shammaah, nass or naswa or niswar (England et al. 2010).
2. Dry snuff: powdered tobacco inhaled through the nose or taken orally.
3. Chewing or sucking tobacco: loose-leaf, plug or twist, a wad of which is placed in the mouth, cheek or inner lip and chewed or sucked (dipped). Also known as 'spit' or 'spitting tobacco'. Regional terms include chimo, toombak, gutkha, twist, pituri or mingkulpa (Ratsch et al. 2010; Shafey et al. 2009).

Compared to the extent of investigation around maternal smoking, research examining the impact of ST use in pregnancy is remarkably scant, this is despite the prevalence of smokeless forms of nicotine in use globally (World Health Organization 2011a). Data from the March 2010 Global Adult Tobacco Survey (GATS) of 14 low and middle income countries estimated that 87.7 million women aged 15+ years used ST compared to 55.6 million women in that same population who smoked cigarettes (Giovino et al. 2012; World Health Organization 2011b). The prevalence of ST use by women in industrialised societies is marginal, although in particular industrialised countries, such as Sweden and Norway, there is increasing usage by women—7 and 6 %, respectively (World Health Organization 2011b). Cognisant that nicotine administered by methods other than smoking is theoretically able to contribute to adverse pregnancy outcomes, England et al. (2010) presented a descriptive summary of the literature. This review extends that summary by undertaking an extensive integrative literature review of oro-nasal ST use in pregnancy.

## Methods

The review methodology (Table 1 Online Resource 1 and Fig. 1 Flow Chart Study Selection) was developed and agreed by the authors prior to commencement and was guided by standards for reporting of observational studies (Moher et al. 2009; Sanderson et al. 2007; Stroup et al. 2000; von Elm et al. 2007). We searched for published and unpublished observational studies from 1966 to 2012 that assessed maternal and perinatal outcomes (Table 2 Online Resource 2) associated with maternal ST exposure. Outcomes considered of high importance were birth outcome, gestational length and birth weight. Searches were conducted in MEDLINE, EMBASE, CINAHL, PsycINFO, Informit Online, WorldCat, Scopus, Proquest Dissertations and Thesis, Australian Digital Thesis, National Library of Australia and Google Scholar. The Boolean key terms were 'tobacco, smokeless' or 'oral', or 'snus' or 'snuff' or 'oral' or 'spit', or 'non-cigarette' combined with 'confinement' or 'pregn*' or mater*' or 'prenat*' or 'child bearing' or ' neonat*' or 'prenatal' or 'baby' or 'babies', or 'foetal', or 'foetal' or 'foetus'. Additional colloquial terms were combined with the pregnancy terms. A manual search of reference lists from retrieved articles, relevant reviews, and potentially relevant web pages was also undertaken. The two reviewers independently screened the full texts for eligibility using a standardized tool, abstracted information and rated the strength of evidence of the eligible studies as a Quality Appraisal Score (QAS) utilizing the Agency for Healthcare Research and Quality (AHRQ) criteria (West et al. 2002). Evidence tables were developed to structure

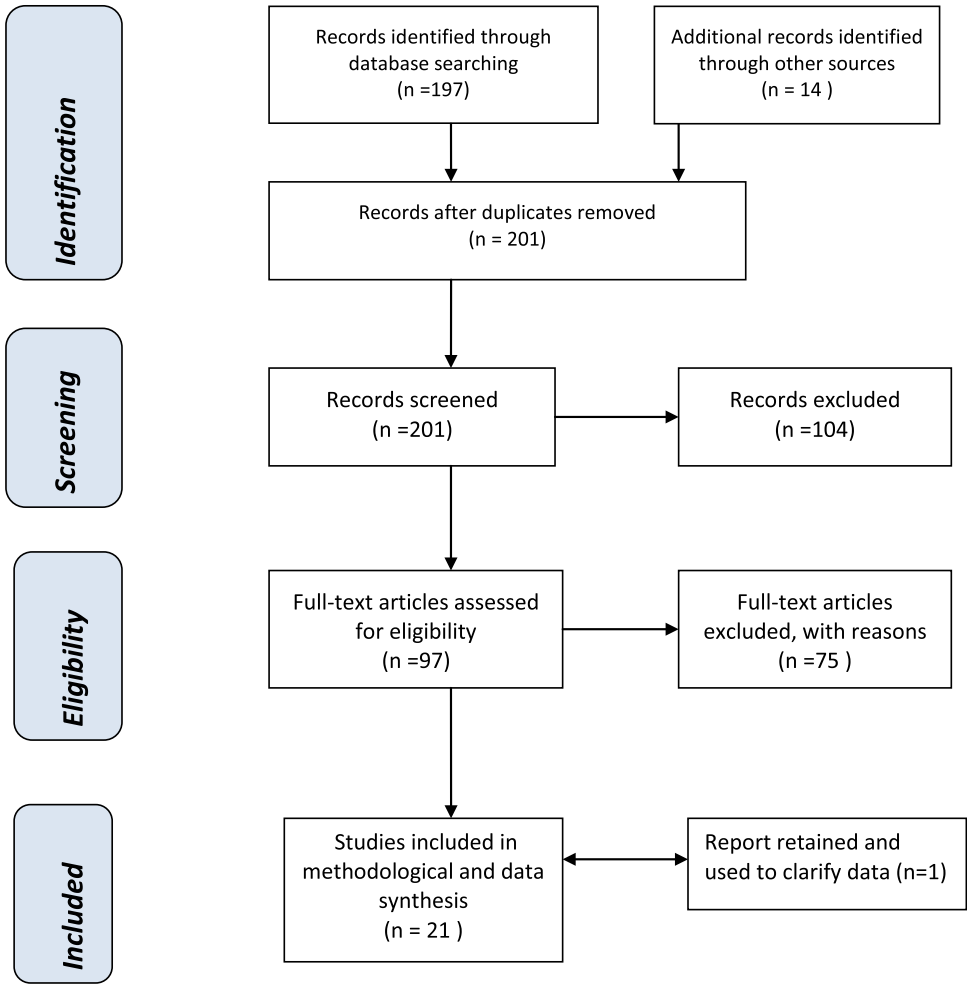


**Fig. 1** Study selection: smokeless tobacco use in pregnancy

the results and due to the heterogeneity of design among the studies, a narrative synthesis was undertaken.

## Results

The results have been summarized into: (a) study characteristics and methodological quality appraisal and (b) clinical outcomes with statistical results. Table 3 (Online Resource 3) details the studies chronologically by country of origin together with the quality assessment criteria and QAS for each element. Final scores ≤50 were considered low reporting quality ($n = 3$). Final scores of 51–70 ($n = 5$) were considered average reporting quality, final scores >71 ($n = 13$) were considered moderate–high reporting quality. Exclusion of the low-scoring studies from further analysis was considered; however, a decision was made to proceed with the broad-based integrative review to ensure inclusion of all available literature on this subject. Table 4 (Online Resource 4) details the descriptive characteristics and findings of the studies.

### Summary: study characteristics and methodological quality appraisal

#### *Population locations and sample size*

Of the 21 included reports, 10 are from India, 7 from Sweden, 2 from Alaska and 1 each from South Africa and Pakistan. Sample size ranged from $n = 40$–782,300.

#### *Study types*

Six small prospective studies (Ashfaq et al. 2008; Dahlstrom et al. 2004; Deshmukh et al. 1998; Hurt et al. 2005; Mehta and Shukla 1990; Verma et al. 1983), four medium prospective population-based studies (England et al. 2003; Gupta and Subramoney 2004, 2006; Subramoney and Gupta 2008), seven larger retrospective population-based studies (Baba et al. 2012; England et al. 2012; Gunnerbeck et al. 2011; Steyn et al. 2006; Wikstrom et al. 2010a, b, c) and one community-based interventional study (Pratinidhi et al. 2010) were included. The reviewers were unable to

ascertain the nature of three studies (Agrawal et al. 1983; Krishna 1978; Sarkar et al. 1992).

*Participant selection, description and comparability*

Several of the studies included smokers, ST users and dual tobacco users and in some studies, the number of ST users was very small. With the exception of the studies by Agrawal et al. (1983, QAS 8), Dahlstrom et al. (2004, QAS 8), Mehta and Shukla (1990, QAS 2) and Sarkar et al. (1992, QAS 1) where there was absent or poorly articulated: participant demographics; group comparisons; and/or participant exclusions, the remaining studies obtained high QAS (≥19/22) for this criteria.

*Exposure and measurement*

There was a consistent 'assumed reader knowledge' of local ST products and their utilization in all the studies resulting in low-average QAS on this element.

- Measurement of exposure was largely based on maternal self-report and/or abstracted from medical records. There was a lack of precision evidence in the measurement of exposure and a lack of consistency across studies resulting in lower QAS for this element.
- Nicotine/cotinine measurement was conducted in only three studies—Sarkar et al. (1992), Dahlstrom et al. (2004) and Hurt et al. (2005) providing those studies with high QAS on this element.

*Pregnancy outcomes*

Perinatal outcomes, specifically: stillbirth, gestational age, anthropometric measurements and gender received the greatest focus in the studies ($n = 17$). Three (3) studies assessed the placenta and several studies described both maternal and perinatal outcomes. Only two (2) studies exclusively measured maternal outcomes. World Health Organization (WHO) or other accepted standardized tools were consistently used to measure outcomes, consequently the QAS for this criteria for all studies (except for Sarkar et al. (1992)—QAS 4) was ≥12/20.

- *Blinding* with the exception of England et al. (2012), none of the studies reported on blinding resulting in QAS of zero on this element.

Summary: clinical outcomes and findings

*Placental findings*

Three studies compared placentas of ST users and non-users. Agrawal et al. (1983) examined 48 varying types of ST users and compared those to 48 non-ST users and reported a statistically significant ($p < 0.005$) increase in mean placental weight (heavier by 65.9 g) in ST consumers. The authors found no difference in mean placental surface area or number of cotyledons. Sarkar et al. (1992), however, reported no difference in gross placental weight or morphology in the placentas ($n = 10$) of Masheri users compared to non-users. Likewise, Ashfaq et al. (2008) confirmed no difference in placental weights and the absence of gross morphological differences in 40 snuff users' placentas compared to 40 non-users' placentas. Ashfaq et al. (2008) however, also undertook micro-morphological inspection and noted highly significant abnormalities in placental structures: (a) doubling of villi with excessive collagen ($p < 0.001$), (b) doubling of sub-trophoblastic basement membrane ($p < 0.001$), (c) doubling of syncytial buds ($p < 0.001$) and (d) tripling of apoptotic cells ($p < 0.001$) in the placentas of ST users.

*Perinatal findings*

Seventeen studies reported on perinatal outcomes broadly categorised: (1) birth outcome (live/stillbirth), (2) foetal distress, neonatal apnoea, early neonatal death and neurobehavioural assessment, (3) gender ratio, (4) gestational age and (5) anthropometric measures.

*Birth outcome (stillbirth)*

Four studies discuss stillbirth. Krishna (1978) reported a stillbirth rate of 50/1,000 births in ST chewers compared to 17/1,000 in non-ST chewers (no $p$ value reported), and Pratinidhi et al. (2010) reported a stillbirth rate of 27/1,000 in ST users compared to 6.0/1,000 in non-users ($p < 0.05$). Gupta and Subramoney (2006) reported 89/1,000 stillbirths in ST users compared to 31/1,000 stillbirths in non-ST users (adjusted odds ratio—AOR: 2.6, 95 % CI 1.4–4.8). The authors described a dose–response relationship between daily frequency of ST use and stillbirth risk [Mishri 1–4 times/day—adjusted hazard risk (AHR) 2.1, 95 % CI 0.9–4.7; Mishri >5 times/day—AHR 3.8, 95 % CI 1.5–10.1]. In Sweden, Wikstrom et al. (2010b) demonstrated a stillbirth rate of 5.2/1,000 in snuff users (OR 1.91, CI 1.4–2.62) compared to a rate of 2.7/1,000 in non-tobacco users.

*Foetal distress, neonatal apnoea, early neonatal death and neurobehavioural assessment*

Hurt et al. (2005) was the only study to report 1 and 5 min Apgar scores and noted no difference between Iqmik users and non-tobacco users. Pratinidhi et al. (2010) observed

that foetal distress occurred at a rate of 14.2 % in Mishri users versus 6.1 % in non-ST user (RR 1.8, 95 % CI 1.06–3.06, $p < 0.05$). Pratinidhi et al. (2010) report the rate of early neonatal deaths in this group of Mishri users was 47/1,000 compared to 17/1,000 in non-ST users, however, contributing factors for these deaths [premature birth, small for gestational age (SGA), foetal distress, foetal abnormalities and pregnancy complications] are not articulated in the paper. Interestingly, Gunnerbeck et al. (2011) reported the incidence of neonatal apnoea in males was 55.5 % compared to 44.4 % females and that both snuff use and smoking were associated with neonatal apnoea in an unadjusted model. Importantly, however, after adjustment (including gestational age), smoking was not associated with apnoea, but the risk of neonatal apnoea with snuff remained (OR 2.24, 95 % CI 1.52–3.32).

While Hurt et al. (2005) recorded equi-prevalent foetal distress in Iqmik-using mothers compared to non-users, they recorded significantly higher ($p < 0.02$) neurobehavioural Lipsitz scores in the neonates of Iqmik-using mothers than in users of other tobacco products and non-tobacco users.

*Gender*

Six papers report gender birth ratios. Krishna (1978) reported a reduced male:female ratio of 80:100 (44.5 % males) in ST chewers compared to 108.5:100 (52 % males) in non-ST users and Mehta and Shukla (1990) reported a similar result of 80.6:100 in ST users of tobacco tooth powder, chewers and smokers compared to 105.5:100 in non-tobacco users. In contrast, Sarkar et al. (1992), England et al. (2003) and Dahlstrom et al. (2004) reported no difference in the gender ratio; however, England et al. (2012) documented the percentage of male:female in continued ST users as 50.6:49.4 compared to 52.1:47.9 in non-tobacco users.

*Gestational age*

Gestational length was considered in nine studies. In Krishna's (1978) cohort of ST chewers, 17.22 % delivered at ≤36 weeks compared to 2.7 % of non-chewers and Gupta and Subramoney (2004) reported 26.7 % of ST users delivering <37 weeks compared to 18.5 % of non-ST users (OR 1.5, 95 % CI 1.009–2.2, $p < 0.05$) and evidence suggestive of a dose–response reduction in gestational age. In contrast, Sarkar et al. (1992) reported all of the neonates ($n = 63$) in their cohort of Masheri users were full-term.

In Sweden, England et al. (2003) examined births from 1999 to 2000 and demonstrated that snuff users accounted for 7.5 % of deliveries <37 weeks (AOR 1.98, 95 % CI 1.46–2.68, $p < 0.0001$) compared to 5.9 % of all smokers (AOR 1.57, 95 % CI 1.38–1.80, $p < 0.0001$) and 3.9 % of non-tobacco users. Wikstrom et al. (2010a) examined the same population from 1999 to 2006 and identified that snuff was associated with increased risk of very (<32 weeks) and moderate (<32–36 weeks + 6 days) preterm birth (AOR 1.25, 95 % CI 1.10–1.41 and 1.33, 95 % CI 1.10–1.61, respectively, $p$ not reported). Gunnerbeck et al. (2011) examined liveborn births between 1999 and 2006 with similar results. Baba et al. (2012) extended the analysis of the same population from 1999 to 2009 and compared cessation in tobacco use during early pregnancy to continued use. They found that the risk of <37 weeks birth in non-users was 4.6 %; with ceased snuff use 4.6 % (AOR 0.71, 95 % CI 0.63–0.81); with ceased smoking 4.7 % (AOR 0.69, 95 % CI 0.66–0.73); with continued snuff use 6.0 % (AOR 1.29 95 % CI 1.17–1.4); and with continued smoking 6.6 % (AOR 1.30 95 % CI 1.25–1.36), $p$ values were not reported.

Similarly, in South Africa, Steyn et al. (2006) identified that users of snuff (ground dried tobacco leaves nasally inhaled or placed in the lower labial vestibule) had shorter gestations than smokers and non-tobacco users ($p < 0.0001$); however, the proportion of neonates from snuff users born <36 weeks was 1.7 % compared to 2.4 % in non-tobacco users and 9.9 % in smokers. Conversely, Hurt et al. (2005) in Alaska found no difference in gestation length with Iqmik use.

*Anthropometric measures*

Twelve studies examined birth weight and, in addition, Krishnamurthy and Joshi (1993) re-report Mehta and Shukla (1990) data correcting an error in the original paper. Krishna (1978) established an adjusted birth weight loss of 100–200 grams (g) in the neonates of ST chewing mothers (p not reported) and Verma et al. (1983) showed an average loss of 395.3 g with ingested tobacco use ($n = 60$, $p < 0.05$) and a non-significant loss in the two (2) users of tobacco tooth powder. In the group of eight (8) tobacco chewers, the average loss compared to non-tobacco users was 449.66 g but recorded as not statistically significant—perhaps due to the small sample size. The daily maternal tobacco consumption threshold whereby a statistically significant ($p < 0.05$) result was evident in birth weight was 200 mg/day. In the Mehta and Shukla (1990) study, the incidence of low birth weight (LBW <2,500 g) in ST users was 64.62 % compared to 36.28 % in non-tobacco users (OR 3.2—no CI reported, $p < 0.001$). Of significance, the authors established that the proportion of LBW females from ST mothers was 56 % compared to 43 % from non-tobacco users—OR 4.08 (adjusted to OR 6.96 by Krishnamurthy and Joshi (1993), $p < 0.0005$). The OR for a LBW male from maternal ST use was 2.09 (adjusted to 1.57 by Krishnamurthy and Joshi

(1993), $p > 0.10$) and not statistically significant. Sarkar et al. (1992) demonstrated an average birth weight loss of 660 g ($p < 0.0001$) in the ST-using group compared to non-users and Gupta and Subramoney (2004) showed a significant ($p < 0.006$) trend of increasing LBW with increased frequency of daily tobacco use. The incidence of LBW in ST users was 28.6 % compared to 19.9 % non-tobacco users—AOR 1.6 (95 % CI 1.1–2.4, $p < 0.05$) with an adjusted average reduction of 87 g in ST users—118 grams in males ($p < 0.05$) and 86 g in females ($p = 0.08$). Deshmukh et al. (1998) showed a prevalence of LBW of 54.1 % with tobacco chewing and passive smoking compared to 32.1 % with no tobacco exposure (OR 3.14, 95 % CI 2.08–4.88, $p < 0.05$). Similarly, Pratinidhi et al. (2010) showed a LBW incidence of 19.3 % compared to 9.0 % in non-tobacco users ($p < 0.05$); however, no difference in birth weight based on frequency of daily tobacco use was determined.

In Sweden, England et al. (2003) documented a non-significant birth weight loss of 93 g; a finding confirmed in the later study by Gunnerbeck et al. (2011) who showed a non-significant SGA rate of 2.4 in snuff users compared to 2.2 in non-users. Similarly, after adjustment, the study by England et al. (2012) with Alaskan Native women showed a non-significant birth weight loss of 78 g with Iqmik use confirming the Hurt et al. (2005) earlier report of no difference in birth weight between tobacco use and non-tobacco users. In South African snuff users, Steyn et al. (2006) observed a non-significant post-adjustment birth weight loss of 17.1 g.

Verma et al. (1983), England et al. (2012) and Hurt et al. (2005) commented on neonatal length and head circumference. Verma et al. (1983) found a decrease in neonatal body length of 0.518 cm with ST use ($p < 0.05$), while England et al. (2012) and Hurt et al. (2005) found no association. No significant difference in mean head circumference was found. Sarkar et al. (1992) was the only study to document chest and abdomen circumference; they commented that the measurements were 'significantly less' in the neonates of ST, however, they did not report a $p$ value.

### *Maternal findings*

Six studies reported on maternal outcomes. Subramoney and Gupta (2008) ascertained that ST use was significantly associated with anaemia (haemoglobin <10.0 g/dl—OR 1.7, 95 % CI 1.2–2.5, $p < 0.0001$), whereas Pratinidhi et al. (2010) reported a statistically insignificant occurrence (11.1 %) of anaemia (haemoglobin <8.0 g/dl) in ST users and 8.6 % in non-users. Pratinidhi et al. (2010) established that the rate of complications in previous pregnancies was higher in ST users ($p < 0.05$) and the rate of complications (except oligohydramnios) during the current pregnancy was higher in ST users (21.1 %) compared to non-users (8.6 %, $p < 0.05$). The authors found pregnancy-induced hypertension (PIH) in users was 2.3 versus 0.4 % in non-users (RR 5.5, 95 % CI 1.06–28.57, $p < 0.05$) and there was an understandable corresponding operative delivery rate of 10.6 % in users compared to 3.9 % in non-users (RR 2.7, 95 % CI 1.46–27.94, $p < 0.05$). A similar increase in the risk of pre-eclampsia was found by England et al. (2003) in Swedish snuff users—AOR 1.58 (95 % CI 1.09–2.27) compared to a reduced risk in smokers—AOR 0.63 (95 % CI 0.53–0.75). Wikstrom et al. (2010c) also demonstrated an increased pre-eclampsia risk in snuff users (AOR 1.1, 95 % CI 0.97–1.28) and a decreased risk with heavy smokers (AOR 0.51, 95 % CI 0.44–0.58). Gunnerbeck et al. (2011) observed that 18.2 % ($p < 0.001$) of snuff users had caesarean deliveries compared to 16.6 % of heavy smokers and 15.4 % of non-tobacco users. In Alaska, Hurt et al. (2005) recorded 22 % ($n = 2$) maternal delivery complications in non-tobacco users; 32 % ($n = 7$) in Iqmik users and 20 % ($n = 2$) in other tobacco users.

### *Correlation of nicotine and cotinine measurements to outcomes*

Sarkar et al. (1992) examined nicotine and cotinine in maternal and cord blood and reported extreme variations in the level of cotinine. Whilst the Dahlstrom et al. (2004) study consisted of only 2 snuff users, both had higher nicotine levels (99 and 89 μg/l) in breast milk samples than the average level for the smokers (57 μg/l). High readings for urinary cotinine were reported in the two neonates of snuff-using mothers (297 and ~125 μg/l, respectively)—the average cotinine level in neonatal urine from smoking and snuff users was 61 μg/l (17–297). Similar findings were identified by Hurt et al. (2005) in the maternal blood of Iqmik users—there were higher concentrations of cotinine compared to participants using other tobacco products (167 ± 116 vs. 81 ± 100 ng/mL). The corresponding cord blood of Iqmik-user mothers had higher concentrations of nicotine (8.4 ± 7.3 vs. 4.4 ± 5.1 ng/mL, $p < 0.05$) and cotinine (153 ± 115 vs. 70 ± 95 ng/mL, $p < 0.05$) compared to participants using other tobacco products.

## Discussion

To the best of our knowledge, this is the first paper to systematically review the literature on ST use and pregnancy outcomes and the likelihood of publication bias is acknowledged. The use of ST by women is largely a phenomenon in less developed regions and research from those regions may not have been published, additionally, unknown colloquial terms for ST will not have been identified as key words in the search.

A major complexity in the examination of the literature was the variety of products described as ST, in addition: different production and curing methods of tobacco; formulations and admixtures; methods of administration; amounts used; frequencies of use; and the combined use of several tobacco products, created impediments to the accurate evaluation of exposure and outcome. Additional complexity arose related in the quantification of exposure: most studies based their data on either self-reported use or documentation from medical records—both of which can result in exposure misclassification (England et al. 2007) and neither of which is equivalent to the biochemical measurement of nicotine or cotinine in biological samples (Cope et al. 2001). Lastly, there is the issue of timing of exposure and dose during the different embryonic and foetal development stages. Determining causality between ST exposure and maternal and perinatal outcomes demands a level of exacting precision that was absent in the reviewed studies. Lastly, the geographical origins of the studies demonstrated marked disparity in the research conduct and reporting rigour undertaken including: enrolment of participants, measurement of variables, control of confounders and modifiers, and levels of analysis undertaken.

Thirteen studies demonstrated a moderate–high level of reporting quality and to different degrees established a range of adverse outcomes associated with ST use in pregnancy. Ashfaq et al. (2008) study provided evidence of significant placental changes—the tripling of apoptosis cells and the replacement of trophoblasts and endothelial cells with fibrous tissue resulting in a thickened placental barrier and a decrease in the functional components of the placenta which ultimately proceed chorionic villi hypoxia. Attention to placental changes in association with ST use is an area for future research.

While marginal birth weight loss was evident with snuff use in Sweden, (England et al. 2003; Gunnerbeck et al. 2011) results from Indian and Pakistan studies (Deshmukh et al. 1998; Gupta and Subramoney 2004; Krishna 1978; Mehta and Shukla 1990; Pratinidhi et al. 2010; Sarkar et al. 1992; Verma et al. 1983) revealed a 10–28 % increase in LBW in ST users compared to non-ST users. The comparison of LBW across diverse cultural and social-economic groups is inherently complex; however, gestational length measures demonstrated increased rates of premature births (<37 weeks) by up to 10 % with ST use compared to non-tobacco users across all cohorts excepting in the Alaskan study by Hurt et al. (2005). Evidence of increased pregnancy complications (Hurt et al. 2005; Pratinidhi et al. 2010; Subramoney and Gupta 2008) and operative deliveries (Gunnerbeck et al. 2011; Pratinidhi et al. 2010) was demonstrated across the varying types of ST users. And, contrary to the effect of smoking in pregnancy, the increase in the incidence of pre-eclampsia (England et al. 2003; Pratinidhi et al. 2010; Wikstrom et al. 2010c) in the differing ST users suggesting that the effect of oral snuff is different to that of combusted tobacco—another area for future research.

Foetal distress and early neonatal death (Pratinidhi et al. 2010), neonatal apnoea (Gunnerbeck et al. 2011) and Lipstiz scores (Hurt et al. 2005) were all doubled in the neonates of ST users. At the same time, the rate of stillbirths in ST users compared to non-tobacco users was at least doubled (Gupta and Subramoney 2006; Krishna 1978; Pratinidhi et al. 2010; Wikstrom et al. 2010b) with a disproportionate increase in the loss of male neonates (England et al. 2012; Gupta and Subramoney 2004, 2006; Krishna 1978; Mehta and Shukla 1990) resulting in a reversal of the male:female birth ratio. Future ST research should include neonatal gender (whether liveborn or stillborn). Dahlstrom et al. (2004) demonstrated that the mean nicotine concentration in the breast milk of snuff users was twice that of smokers and a corresponding high urine nicotine level in the neonates of snuff-using mothers together with similar findings in the Hurt et al. (2005) study of Alaskan Native Iqmik users raises questions about the volume, the dose and the pharmacodynamics and kinetics of nicotine ingested through breast milk. Longitudinal follow-up of neonatal growth and development parameters and particularly the incidence of Sudden Infant Death Syndrome (SIDS) in the children of ST users will provide further insight.

Evidence of dose/type of tobacco-dependent increase in foeto-toxicity and pregnancy complications was demonstrated in some of the studies (Agrawal et al. 1983; Gupta and Subramoney 2004, 2006; Mehta and Shukla 1990; Verma et al. 1983; Wikstrom et al. 2010a, b, c), however, consideration of these finding was severely hampered due to the changing effects of nicotine through each stage of foetal development and pregnancy and by the lack of precision around nicotine administration technique, the volume, frequency, formulation and nicotine content of the ST. The most accurate estimate of exposure is provided by measurement of nicotine, albeit that measurement only demonstrates recency of exposure due to the short half-life of nicotine (Benowitz et al. 2009); however, in clinical practice, ST use should be recorded at each antenatal visit and changes in use should be recorded through the duration of the pregnancy.

In the reviewed papers, construct validity is undoubtedly the missing evidentiary element. Without a reliable and valid measurement of nicotine exposure, the underlying foundation for each study is reliant upon both participant and observer factors, and thus chance, bias and confounding can all be argued as being responsible for the

outcomes. Biological measurement of nicotine and cotinine in a range of maternal and neonatal biological material is needed to provide accurate measures of exposure, absorption, metabolism and excretion of nicotine absorbed through ST use, this then matched to maternal and neonatal outcomes will provide a basis for beginning to consider the effects of maternal ST use on pregnancy outcomes. Minimum details required to assess exposure accurately would include: formulation, admixtures, nicotine content, volume of ST per use, frequency of use, administration techniques, biological site(s) of administration, duration of each exposure, retention of tobacco including overnight retention, and expectoration versus swallowing saliva. Additionally, specific information about gestational age and changes to administration of nicotine during pregnancy are required.

Whilst some of the outcomes and risks reported in the reviewed papers may also be explained by differences in the populations including genetic, socio, economic, education, cultural and anthropometric parameters, and differences in access and level of health care and pregnancy and birth management, what is evident is that nicotine is self-administered by methods other than inhalation by many women during pregnancy and lactation and clearly, maternal oro-nasal absorption of nicotine initiates a range of responses in the mother, the placenta, and neonate.

## Future research agenda

Gunnerbeck et al. (2011) comment that the number of female snuff users has more than tripled during the last decade in Sweden, and according to WHO (World Health Organization 2011b), the rate of ST use globally is increasing and moving into traditional smoking populations. The United States has seen an increase in ST use by 9 % each year over recent years (Burritt and Gustafsson 2013) largely driven by the public health education and legislative changes surrounding smoking. Previously ST use would have been considered an idiosyncratic phenomena and of interest to healthcare providers primarily working in developing nations. However, healthcare providers in developed countries are now compelled to take a broader perspective on nicotine adminstration (including ST use and other non-combusted forms including nicotine patches, gum, lozenges, mists and spray) and, accordingly, consider the outcomes of maternal ST use in pregnancy.

Evidence from this integrative review provides specific areas for further research, and combined with the magnitude of evidence generated from the 'smoking in pregnancy' research, a platform for directing and targeting future research can be established.

**Acknowledgments** AR is supported by a Queensland Health—Office of Health and Medical Research Fellowship, The University of Queensland—School of Nursing and Midwifery-Elizabeth A. Davies Scholarship, and the Queensland Centaur Memorial Fund for Nurses Scholarship. The University of Queensland has provided a FirstLink Grant to the larger program of research of which this review forms a part.

## References

Aagaard-Tillery KM, Porter TF, Lane RH, Varner MW, Lacoursiere DY (2008) In utero tobacco exposure is associated with modified effects of maternal factors on fetal growth. Am J Obstet Gynecol 198 (1):66 e61–66. doi:10.1016/j.ajog.2007.06.078

Agrawal P, Chansoriya M, Kaul KK (1983) Effect of tobacco chewing by mothers on placental morphology. Indian Pediatr 20(8):561–565

Ashfaq M, Channa MA, Malik MA, Khan D (2008) Morphological changes in human placenta of wet snuff users. J Ayub Med Coll Abbottabad: JAMC 20(2):110–113

Baba S, Wikstrom AK, Stephansson O, Cnattingius S (2012) Influence of smoking and snuff cessation on risk of preterm birth. Eur J Epidemiol 27(4):297–304. doi:10.1007/s10654-012-9676-8

Benowitz NL, Porchet H, Sheiner L, Jacob P (1988) Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. Clin Pharmacol Ther 44(1):23–28. doi:10.1038/clpt.1988.107

Bruin JE, Gerstein HC, Holloway AC (2010) Long-term consequences of fetal and neonatal nicotine exposure: a critical review. Toxicol Sci 116(2):364–374. doi:10.1093/toxsci/kfq103

Burritt C, Gustafsson K (2013) Sweden's Snus tobacco invades, but Americans Prefer Snuff. http://www.businessweek.com/articles/2013-07-03/swedens-snus-tobacco-invades-but-americans-prefer-snuff. Accessed 1 Aug 2013

Caldwell B, Sumner W, Crane J (2012) A systematic review of nicotine by inhalation: is there a role for the inhaled route? Nicotine Tob Res 14(10):1127–1139. doi:10.1093/ntr/nts009

Cope GF, Nayyar P, Holder R (2001) Measurement of nicotine intake in pregnant women—associations to changes in blood cell count. Nicotine Tob Res 3(2):119–122. doi:10.1080/14622200110042645

Dahlstrom A, Ebersjo C, Lundell B (2004) Nicotine exposure in breastfed infants. Acta Paediatr 93(6):810–816. doi:10.1111/j.1651-2227.2004.tb03023.x

Deshmukh JS, Motghare DD, Zodpey SP, Wadhva SK (1998) Low birth weight and associated maternal factors in an urban area. Indian Pediatr 35(1):33–36

England LJ, Levine RJ, Mills JL, Klebanoff MA, Yu KF, Cnattingius S (2003) Adverse pregnancy outcomes in snuff users. Am J Obstet Gynecol 189(4):939–943. doi:10.1067/S0002-9378(03)00661-6

England LJ, Grauman A, Qian C, Wilkins DG, Schisterman EF, Yu KF, Levine RJ (2007) Misclassification of maternal smoking status and its effects on an epidemiologic study of pregnancy outcomes. Nicotine Tob Res 9(10):1005–1013. doi:10.1080/14622200701491255

England LJ, Kim SY, Tomar SL, Ray CS, Gupta PC, Eissenberg T, Cnattingius S, Bernert JT, Tita AT, Winn DM, Djordjevic MV, Lambe M, Stamilio D, Chipato T, Tolosa JE (2010) Non-cigarette tobacco use among women and adverse pregnancy outcomes. Acta Obstet Gynecol Scand 89(4):454–464. doi:10.3109/00016341003605719

England LJ, Kim SY, Shapiro-Mendoza CK, Wilson HG, Kendrick JS, Satten GA, Lewis CA, Whittern P, Tucker MJ, Callaghan WM (2012) Maternal smokeless tobacco use in Alaska Native women and singleton infant birth size. Acta Obstet Gynecol Scand 91(1):93–103. doi:10.1111/j.1600-0412.2011.01273.x

Ginzel KH, Maritz GS, Marks DF, Neuberger M, Pauly JR, Polito JR, Schulte-Hermann R, Slotkin TA (2007) Critical review: nicotine for the fetus, the infant and the adolescent? J Health Psychol 12(2):215–224. doi:10.1177/1359105307074240

Giovino GA, Mirza SA, Samet JM, Gupta PC, Jarvis MJ, Bhala N, Peto R, Zatonski W, Hsia J, Morton J, Palipudi KM, Asma S (2012) Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys. Lancet 380(9842):668–679. doi:10.1016/s0140-6736(12)61085-x

Gunnerbeck A, Wikstrom AK, Bonamy AK, Wickstrom R, Cnattingius S (2011) Relationship of maternal snuff use and cigarette smoking with neonatal apnea. Pediatrics 128(3):503–509. doi:10.1542/peds.2010-3811

Gupta PC, Subramoney S (2004) Smokeless tobacco use, birth weight, and gestational age: population based, prospective cohort study of 1217 women in Mumbai, India. BMJ 328(7455):1538. doi:10.1136/bmj.38113.687882.EB

Gupta PC, Subramoney S (2006) Smokeless tobacco use and risk of stillbirth. Epidemiology 17(1):47–51. doi:10.1097/01.ede.0000190545.19168.c4

Hurt RD, Renner CC, Patten CA, Ebbert JO, Offord KP, Schroeder DR, Enoch CC, Gill L, Angstman SE, Moyer TP (2005) Iqmik—a form of smokeless tobacco used by pregnant Alaska natives: nicotine exposure in their neonates. J Matern Fetal Neonatal Med 17(4):281–289. doi:10.1080/14767050500123731

Benowitz NL, Hukkanen J, Jacob P, III (2009) Nicotine chemistry, metabolism, kinetics and biomarkers. In: Henningfield JE, London ED, Pogun S (eds) Nicotine psychopharmacology, vol 192. Handbook of experimental pharmacology. Springer, Berlin, pp 29–60. doi:10.1007/978-3-540-69248-5_2

Jauniaux E, Burton GJ (2007) Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. Early Human Dev 83(11):699–706. doi:10.1016/j.earlhumdev.2007.07.016

Khalki H, Khalki L, Aboufatima R, Ouachrif A, Mountassir M, Benharref A, Chait A (2012) Prenatal exposure to tobacco extract containing nicotinic alkaloids produces morphological and behavioral changes in newborn rats. Pharmacol Biochem Behav 101(3):342–347. doi:10.1016/j.pbb.2012.01.020

Krishna K (1978) Tobacco chewing in pregnancy. Br J Obstet Gynaecol 85(10):726–728. doi:10.1111/j.1471-0528.1978.tb15591.x

Krishnamurthy S, Joshi S (1993) Gender differences and low birth weight with maternal smokeless tobacco use in pregnancy. J Trop Pediatr 39(4):253–254. doi:10.1093/tropej/39.4.253

Lambers DS, Clark KE (1996) The maternal and fetal physiologic effects of nicotine. Semin Perinatol 20(2):115–126. doi:10.1016/S0146-0005(96)80079-6

Law KL, Stroud LR, LaGasse LL, Niaura R, Liu J, Lester BM (2003) Smoking during pregnancy and newborn neurobehavior. Pediatrics 111(6 Pt 1):1318–1323. doi:10.1542/peds.111.6.1318

Mehta A, Shukla S (1990) Tobacco and pregnancy. J Obstet Gynaecol India 40(2):156–160

Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62(10):1006–1012

Pratinidhi A, Gandham S, Shrotri A, Patil A, Pardeshi S (2010) Use of 'Mishri' a smokeless form of tobacco during pregnancy and its perinatal outcome. Indian J Commun Med 35(1):14–18. doi:10.4103/0970-0218.62547

Ratsch A, Steadman KJ, Bogossian F (2010) The pituri story: a review of the historical literature surrounding traditional Australian Aboriginal use of nicotine in Central Australia. J Ethnobiol Ethnomed 6:26. doi:10.1186/1746-4269-6-26

Reeves S, Bernstein I (2008) Effects of maternal tobacco-smoke exposure on fetal growth and neonatal size. Expert Rev Obstetr Gynecol 3(6):719–730. doi:10.1586/17474108.3.6.719

Richter P, Spierto FW (2003) Surveillance of smokeless tobacco nicotine, pH, moisture, and unprotonated nicotine content. Nicotine Tob Res 5(6):885–889. doi:10.1080/1462220031000161464 7

Rogers JM (2009) Tobacco and pregnancy. Reprod Toxicol 28(2):152–160. doi:10.1016/j.reprotox.2009.03.012

Sanderson S, Tatt ID, Higgins JP (2007) Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol 36(3):666–676. doi:10.1093/ije/dym018

Sarkar S, Bhide M, Bhide A, Raghavan S, Maru G, Bhide S (1992) Transplacental exposure of human foetuses to nicotine/cotinine in masheri addict mothers and consequent loss of weight in babies at birth. Paper presented at the Nitroso Compounds: Biological Mechanisms, Exposures and Cancer Etiology Conference, Kailua-Kona, Hawaii, USA, November 1–2, 1991

Shafey O, Eriksen M, Ross H, Mackey J (2009) The tobacco atlas. American Cancer Society. http://www.afro.who.int/en/clusters-a-programmes/hpr/health-risk-factors/tobacco/tobacco-country-profiles.html. Accessed 20 June 2013

Slotkin T (1997) Expert opinions: Nicotine: interview with professor theodore slotkin. ABC Online—Quantum. Australia Broadcasting Corporation, Australia

Slotkin TA, Lappi SE, McCook EC, Lorber BA, Seidler FJ (1995) Loss of neonatal hypoxia tolerance after prenatal nicotine exposure: implications for sudden infant death syndrome. Brain Res Bull 38(1):69–75. doi:10.1016/0361-9230(95)00073-N

Slotkin TA, McCook EC, Seidler FJ (1997) Cryptic brain cell injury caused by fetal nicotine exposure is associated with persistent elevations of c-fos protooncogene expression. Brain Res 750(1–2):180–188. doi:10.1016/S0006-8993(96)01345-5

Steyn K, de Wet T, Saloojee Y, Nel H, Yach D (2006) The influence of maternal cigarette smoking, snuff use and passive smoking on pregnancy outcomes: the Birth to Ten Study. Paediatr Perinat Epidemiol 20(2):90–99. doi:10.1111/j.1365-3016.2006.00707.x

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 283(15):2008–2012. doi:10.1001/jama.283.15.2008

Subramoney S, Gupta PC (2008) Anemia in pregnant women who use smokeless tobacco. Nicotine Tob Res 10(5):917–920. doi:10.1080/14622200802027206

Verma RC, Chansoriya M, Kaul KK (1983) Effect of tobacco chewing by mothers on fetal outcome. Indian Pediatr 20(2):105–111

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Epidemiology 18(6):800–804. doi:10.1097/EDE.0b013e3181577654

West S, King V, Carey T, Lohr K, McKoy N, Sutton S, Lux L (2002) Systems to rate the strength of scientific evidence. Evidence Report/Technology Assessment No. 472002. (trans: U.S. Department of Health and Human Services), Rockville

Wikstrom AK, Cnattingius S, Galanti MR, Kieler H, Stephansson O (2010a) Effect of Swedish snuff (snus) on preterm birth. BJOG 117(8):1005–1010. doi:10.1111/j.1471-0528.2010.02575.x

Wikstrom AK, Cnattingius S, Stephansson O (2010b) Maternal use of Swedish snuff (snus) and risk of stillbirth. Epidemiology 21(6):772–778. doi:10.1097/EDE.0b013e3181f20d7e

Wikstrom AK, Stephansson O, Cnattingius S (2010c) Tobacco use during pregnancy and preeclampsia risk: effects of cigarette smoking and snuff. Hypertension 55(5):1254–1259. doi:10.1161/HYPERTENSIONAHA.109.147082

World Health Organization (2011a) WHO Report on the global tobacco epidemic, 2011: warning about the dangers of tobacco. World Health Organisation, Geneva

World Health Organization (2011b) Crude smokeless tobacco prevalence in WHO member states. World Health Organisation, Geneva