Smokeless tobacco consumption and stillbirth: Case-control study in Bangladesh

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Abstract

Aims: To investigate the association between smokeless tobacco consumption (STC) during pregnancy and risk of stillbirth.

Design and Methods: We conducted a population-based case-control study of 253 cases and 759 randomly selected control women in Madaripur, Bangladesh. We conducted a survey of two rural local government areas including 8082 married women (99.9% response) and identified cases based on self-report of a stillbirth outcome of the participants' first pregnancy. All were asked about STC during their first pregnancy and a range of risk markers and known confounders. Demographic and maternal variables associated ($p<0.25$) either with stillbirth or STC were included in logistic regression models.

Results: Of the 241 cases and 757 controls with complete exposure data, 32 cases (13.2%) and 18 controls (2.4%) used smokeless tobacco during pregnancy (OR=6.28; 95% CI: 3.45–11.4). After adjustment for education, household income, age at first pregnancy, vaccination during pregnancy, complications, exposure to arsenic in the drinking water, place of delivery, and antenatal care, excess risk was attenuated but remained significant (aOR 2.87; 95% CI: 1.36–6.08). There was a dose-effect association, with women who used smokeless tobacco >5 times daily during their first pregnancy at greater risk of having a stillbirth (aOR=5.89; 95% CI: 1.70–20.3) than less frequent users (aOR 1.67; 95% CI: 0.65–4.29). The estimates were robust to extreme assumptions about missing exposure data.

Conclusions: STC during pregnancy increases the risk of a stillbirth. Smokeless tobacco control strategies are urgently needed in South Asia.

Key words: smokeless tobacco, chewing tobacco, stillbirth, rural, Bangladesh.

Introduction

Smokeless tobacco consumption (STC) is a public health issue in many countries, especially in South Asia [1-2]. Smokeless tobacco products are cheaper than cigarettes, and are perceived by some as a harmless alternative to smoking [3-4]. In some countries, STC is an acceptable cultural norm [2, 5]. More than one third of total tobacco consumption in South Asia is in the form of chewing tobacco [2]. The WHO estimates that there are nearly 250 million adult smokeless tobacco users in South Asia (including 26 million in Bangladesh) representing 90% of global smokeless tobacco consumers [6-8]. In Bangladesh, the prevalence of smoking among women (1.5%) is very low compared to men (45%) whereas STC is similarly common among women (28%) and men (26%) [3, 9].

The perinatal mortality rate in India and Bangladesh stands at 65-80/1000 births, in comparison to 20-25/1000 births in Sri lanka and Thailand, and 3-5/1000 births in high income countries [10]. Two thirds (66%) of all stillbirths occur in only 10 countries, including Bangladesh [11]. The highest rates occur in Pakistan (47/1000 births), Nigeria (42/1000 births) and Bangladesh (36/1000 births) [11]. The estimated trend in stillbirth rate reduction is slower than that of maternal mortality and lags behind rapid progress in reducing deaths in children younger than 5 years [11].

Studies from various countries indicate that STC is a risk factor for cancer of the oral cavity [12-14], throat, head, and neck [14-15]. It also increases the risk of pancreatic cancer, diabetes, metabolic disease, and cardiovascular disease [12, 16-18], stroke, high cholesterol, and adverse pregnancy outcomes [12, 16, 18-20].

Many studies have been conducted on smoking and stillbirth but only a few have investigated the association between STC and stillbirth [12, 15, 18], and the evidence of an association remains inconclusive [12, 15]. The prevalence of current STC and risk of stillbirth among women in South Asia are very high compared to developed countries [19-21]. Only two studies so far have examined the association between STC and adverse pregnancy outcomes in Bangladesh [22-23], and each had limitations in outcome measurement and statistical analysis. They did not measure the association between dose of STC and adverse pregnancy outcomes and they failed to account for several known confounders. In this study, we estimate the risk of stillbirth among Bangladeshi rural women during their first pregnancy.

Materials and Methods

Ethical approval

We obtained ethical approval from the University of Newcastle's Human Research Ethics Committee, Australia (H-2011-0131) and from the Bangladesh Medical Research Council. An information sheet describing the purpose of the study and individuals' rights as participants was handed to the women to read. For individuals with inadequate literacy, the information sheet was read out by the interviewers. Informed consent was then obtained from each person. A thumb impression was provided by those unable to sign the consent form.

Design

We conducted a population based case-control study.

Study area and population

We initially conducted a baseline survey in two Local Government Areas (LGAs): Jhaudi and Ghotmajhi, of the Madaripur district, and identified 8082 women aged 18 years and older

who had ever married, with at least one pregnancy in their lifetime. Details of the baseline survey have been described elsewhere [7]. Among those women 253 had a history of stillbirth in their first pregnancy.

Selection of Cases and Controls

Selection criteria of the cases were (i) being 18 years or older, (ii) having been married with a stillbirth in their first pregnancy, and (iii) willingness to participate. The selection criteria for the controls were (i) being 18 years or older, (ii) having been married with no stillbirth in their first pregnancy, and (iii) willingness to participate. We recruited 253 cases after excluding 88 women with a history of stillbirth but not in their first pregnancy, and we randomly selected 759 controls randomly from the remaining 7733 women with a case:control ratio of 3: 1 (Figure 1). The sample size is sufficient to estimate an odds ratio of 1.5 with 95% confidence and 80% power.

[Please insert Figure 1 here]

Data collection procedures

After obtaining informed consent, information was collected on socio-economic status and demography, history of STC and information regarding outcomes of their first pregnancy using an interviewer administered questionnaire by face-to-face interview. A quality control team was formed by the investigators to monitor the performance of field personnel and supervisors through regular observation at the household level and regular cross-checking of data for completeness. In 5% of study participants, the quality control team repeated data collection independently. Identified errors were corrected immediately in the field. Weekly staff meetings were held to review the progress of the study. During data collection the team

contacted the Health and Family Planning Officer, other officials of the LGAs, and local leaders, and also at the village level to facilitate the cooperation of local people.

Exposure assessment

Each participant's self-reported STC during their first pregnancy was ascertained during the interview. We categorized the exposure variable as 'No' or 'Yes', based on STC exposure. Then we categorized the exposed category by dose '1–5 times daily' or '>5 times daily'.

Outcome definitions

Any fetus that did not breathe or show other evidence of life at birth after a minimum 28 weeks of gestation based on the mother's report was defined as a stillbirth [24]. Gestational age at delivery was determined on the basis of the mother's response regarding the number of days from the start of the last normal menstrual period to delivery.

Statistical analyses

Data were analysed using Stata version 12 [25]. We calculated descriptive statistics for demographic variables by case-control status. Categorical variables were compared using Pearson's chi-square test. For categorical variables we reported missing values as a separate category. Our main exposure variable was binary (smokeless tobacco user / non-user). We conducted univariable logistic regression analysis with potential confounders. In the final linear models, we only included those variables found to be significant at $P < 0.25$ level in the initial models to accommodate more explanatory variables in the final model and to reduce type II error. To determine the association between STC and stillbirth after adjusting for potential confounders, we adopted a backward elimination approach. From the base model, we first excluded the variable that had the highest P-value above 0.05 and checked its

confounding effect by comparing the odds ratio of STC before and after exclusion of that variable. We considered the variable as a confounder if the OR changed by 10% due to exclusion of the variable from the model. If the variable was not a confounder and it yielded a *P>0.05* from the likelihood ratio test we excluded the variable from the model. We repeated the same process for all other potential confounders according to their P-values in the multivariable model. If a variable was not a confounder but was significant (5% level) we kept the variable in the model. After deciding the final model following this procedure we checked for multicollinearity by estimating the variance inflation factor (VIF). A VIF of >10 was considered indicative of multicollinearity between two or more variables. In such a situation, a decision was made on which of the collinear variables to keep based on their clinical importance. Since VIF cannot be estimated from logistic regression we fitted a multivariable linear regression model only for the purpose of estimating VIFs. We also checked for dose-response effects in the final multivariable model by replacing the binary exposure variable with a three level ('No' exposure, '1-5 times daily' and '>5 times daily') ordinal categorical variable. We checked for both linear and quadratic trend using the *p.contrast* command in Stata v12 after running the logistic regression model.

Results

The population survey from which 253 cases and 759 controls were drawn had a response rate e.g. 99.9% (8074/8082) [7]. The cases were not similar to the controls with respect to age, education, marital status, and household income, current STC, STC during first pregnancy, age at first pregnancy, prevalence of smoking, exposure to second hand smoke at home, antenatal care, and arsenic in drinking water. Cases were older, less educated, and poorer, had a higher prevalence of current STC and used a larger dose during their first pregnancy than controls. A larger population of the cases did not receive antenatal care

during their first pregnancy compared to controls. Most of the participants had given birth to their baby at home (95% of cases and 92% of controls). In the univariate analysis, low income, age at first pregnancy, place of delivery and STC were associated with stillbirth (Table 1).

[Please insert Table 1 here]

Of the 241 cases and 757 controls with complete exposure data, 32 cases (13.2%) and 18 controls (2.4%) used smokeless tobacco during pregnancy (OR=6.28; 95% CI: 3.45–11.4). After adjustment for education, household income, age at 1st pregnancy, vaccination during pregnancy, complications during pregnancy, exposure to arsenic in the drinking water, place of delivery, and antenatal care, excess risk was attenuated but remained significant (aOR 2.87; 95% CI: 1.36–6.08). There was a dose-effect association, with women who used smokeless tobacco >5 times daily during their first pregnancy at greater risk of having a stillbirth (aOR=5.89; 95% CI: 1.70–20.3) than less frequent users (aOR 1.67; 95% CI: 0.65–4.29).

[Please insert Table 2 here]

Sensitivity analysis

There were 12 cases and two controls with missing exposure data (Table 1). For the purpose of determining the sensitivity of the risk estimate to those missing data, we calculated odds ratios under extreme assumption (1) that all missing cases were exposed to STC and all missing controls were not exposed; and (2) that all missing cases were not exposed to STC while all controls were exposed. Under the first assumption the adjusted odds of stillbirth

were 3.9 times (95% CI: 1.90 – 7.55) higher than those for non-users while under the second assumption, the adjusted odds were 2.8 times (95% CI: 1.37 – 5.62) higher showing that the risk estimates were robust.

Discussion

STC during pregnancy increases the risk for stillbirth with some evidence of a dose-related effect, independent of known confounders. This risk is larger than the effect of maternal smoking for which the relative risk of stillbirth ranges from 1.2 to 1.6 [26].

This is a unique piece of research in this area in that it was a large, population-based, case-control study. All data were collected without knowledge of outcome and by well-trained interviewers using face-to-face interviews. A quality control team monitored the entire data collection process and repeated 5% of study participants' interviews for cross-checking of data. We conducted a baseline survey among 8082 participants for identifying cases and controls. Therefore, we had enough controls to select participants randomly from the representative sample. We performed rigorous analyses of associations with control for a large number of known and suspected confounders.

The main limitation of the study is the absence of clinical documentation of pregnancy outcomes and related causes of stillbirth. Accordingly, we had to rely on respondents' self-reports for measuring the outcomes, exposure, and potential confounders. We expect that an outcome such as stillbirth is unlikely to be forgotten or differentially reported by mothers in the context of a confidential study.

There is, however, a risk of recall error about STC during pregnancy. We do not know of empirical evidence bearing on whether women would accurately recall and report their STC during pregnancy, however, it should be noted that there is no taboo against STC among women in South Asia [2]. Accordingly, misreporting, if any, is likely to be non-differential and therefore would underestimate the association between STC and stillbirth.

Other limitations of this study include variation in the amount of nicotine in different types of smokeless tobacco product. It was beyond the scope of the study to measure the amount of nicotine and we had to rely on participants' reports of their frequency of consumption to measure the dose. The association between STC and risk of stillbirth may be confounded by other factors causally related to the outcome that we are unaware of or did not measured. We adjusted for all known confounders except nutritional status. It was considered infeasible to retrospectively obtain measures of nutritional status during first pregnancy. Being a population based study almost with 100% participation means the results are not biased by various selection processes.

Our findings are consistent with those of other studies. In the best of these, a cohort of 1217 pregnant women in Mumbai, India, the cumulative incidence of stillbirth was significantly higher among smokeless tobacco users than among non-users (8.9 vs. 3.1%) with an adjusted Cox proportional hazards ratio of 2.6 (95% CI: 1.4 – 4.8) [15]. A hospital-based cross-sectional study conducted in Pune, India, revealed that the risk of stillbirth was 3 times higher (5.0 vs. 1.7%) among tobacco chewers than in non-chewers [12]. Two Bangladeshi studies have been conducted with unadjusted odds ratios of around 2 for the risk of stillbirth with STC during pregnancy [22-23].

Adverse pregnancy outcomes of tobacco smoking have been studied widely and smoking during pregnancy is established as a cause of stillbirth [27], however, the biologic mechanisms by which STC might cause stillbirth are yet to be fully elucidated [27]. Heavy metals such as lead and cadmium, which have been found in smokeless tobacco, present potential risks to the fetus [28]. Furthermore, exposure to cotinine in the fetuses of smokeless tobacco consumers has been reported [28], indicating that nicotine and perhaps other toxic substances can cross the placental barrier [16, 28]. STC during pregnancy has also been linked with growth restriction [13], preterm delivery [13], anemia [29] and placental morphologic changes [14]. These mechanisms may increase the risk of stillbirth from STC. Also, nicotine may induce changes in the central respiratory control mechanism and elicit fetal hypoxia-ischemia [30]. Smokeless tobacco consumers have significantly higher numbers of chorionic villi with excessive collagen, higher incidence of apoptosis in parenchymal cells, higher density of syncytial knots, and thicker subtrophoblastic basement membrane compared to non-users [14, 31]. Such changes could increase the risk of adverse birth outcomes [14, 31].

Conclusions

In summary, our data are consistent with accumulating evidence that STC during pregnancy is associated with increased risk of stillbirth. Smokeless tobacco control strategies should be implemented urgently in Bangladesh especially targeting women of child bearing age.

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Author Contributions

MSH, KK, BR and AHM participated in the design of the study. MSH, SA and BR managed the dataset and performed statistical analyses. AHM and KK gave advice regarding the statistical analyses. All authors contributed to the interpretation of the results, as well as to the writing and editing of the manuscript.

Disclosure of interest

None to declare.

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Figure 1: Selection process of cases and controls.

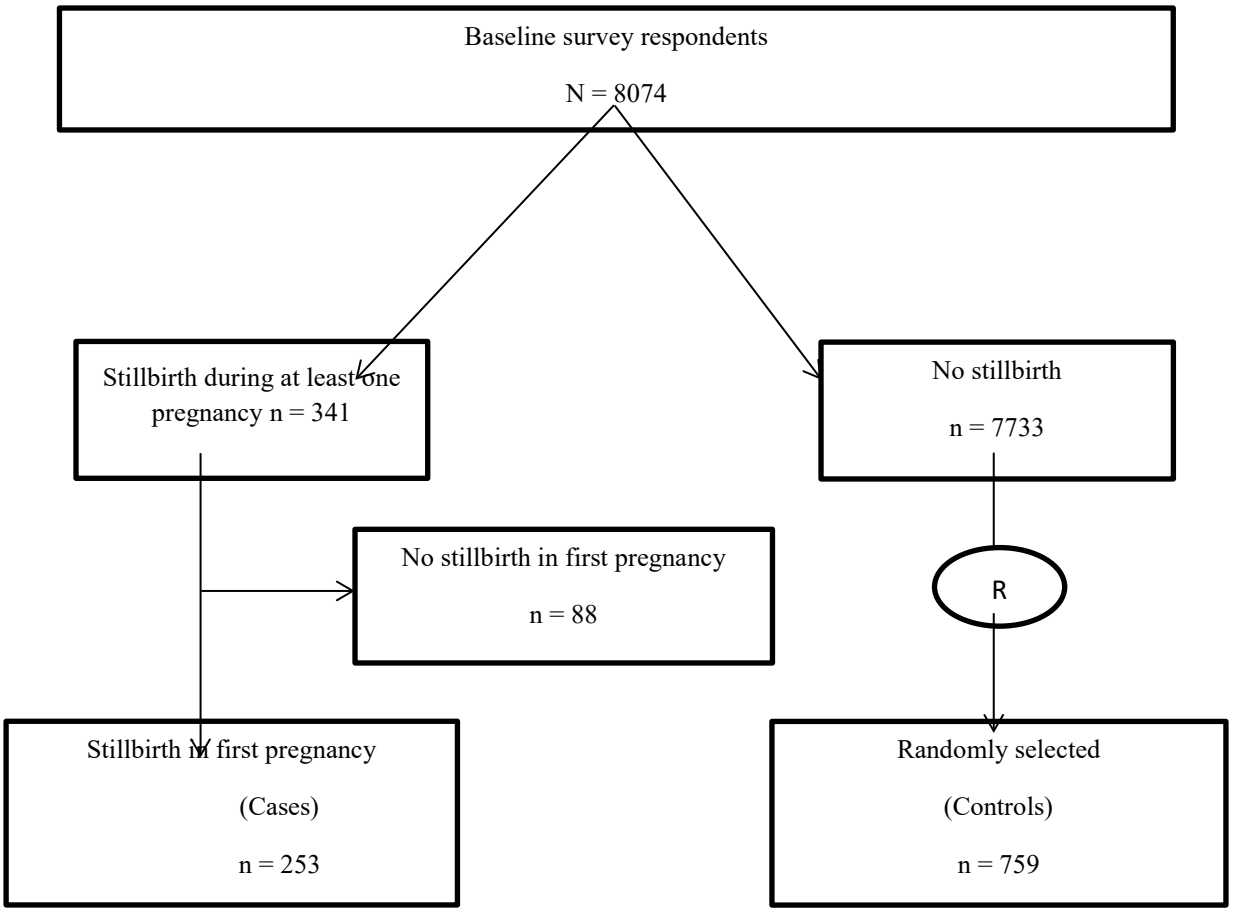

Table 1: *Characteristics of the cases and controls and unadjusted associations with stillbirth (N=1012)*

Characteristics, n (%)	Cases (n=253)	Controls (n=759)	Unadjusted Odds Ratio (95% CI)	*p*
Current age (years)				
Mean (Standard deviation)	37.6 (12.8)	35.1 (13.4)		
≤ 24 years	28 (11.1)	159 (20.9)	1	
25 – 44	159 (62.9)	421 (55.5)	2.14 (1.37 – 3.33)	*0.002*
≥45 years	66 (26.0)	179 (23.6)	2.09 (1.28 – 3.42)	
Level of education				
Tertiary	3 (1.2)	31 (4.1)	1	
Secondary	45 (17.8)	201 (26.5)	2.31 (0.67 – 7.90)	
Primary	64 (25.3)	244 (32.2)	2.71 (0.80 – 9.14)	*<0.001*
No formal education	141 (55.7)	283 (37.2)	5.14 (1.54 – 17.1)	
Occupation				
Housewife	247 (97.6)	730 (96.2)	1	
Employed	2 (0.8)	15 (1.9)	1.07 (0.34 – 3.41)	
Unemployed	4 (1.6)	11 (1.5)	0.39 (0.08 – 1.74)	*0.45*
Missing	0 (0.0)	3 (0.04)		
Monthly household income (US$)				
>$150	43 (17.0)	282 (37.2)	1	
$100 - $150	78 (30.8)	249 (32.8)	2.05 (1.36 – 3.09)	*<0.001*
<$100	113 (44.7)	219 (28.9)	3.38 (2.28 – 5.01)	
Missing	19 (7.5)	9 (1.1)		
STC				
Never consumed	63 (24.9)	324 (42.7)	1	
Ex-consumer	68 (26.9)	256 (33.7	1.36 (0.93 – 1.99)	*<0.001*
Current consumer	122 (48.2)	179 (23.6)	3.50 (2.45 – 4.99)	
STC during pregnancy				
No	209 (82.6)	739 (97.4)	1	
Yes	32 (12.6)	18 (2.4)	6.28 (3.45 – 11.4)	*<0.001*
Missing	12 (4.8)	2 (0.2)		
Dose during pregnancy				
None	221 (87.4)	741 (97.6)	1	
1 – 5 times daily	16 (6.3)	13 (1.7)	4.12 (1.95 – 8.71)	*<0.001*
>5 times daily	16 (6.3)	5 (0.7)	10.7 (3.88 – 29.6)	
Age at 1st pregnancy (years)				
≥23 years	5 (1.9)	40 (5.3)	1	
18 – 22	127 (50.2)	382 (50.3)	2.65 (1.02 – 6.88)	*<0.001*
<18 years	121 (47.8.0)	337 (44.4)	2.78 (1.10 – 7.44)	
Smoking				
Never smoked	230 (90.9)	751 (99.0)	1	
Ex-smoker	11 (4.4)	3 (0.4)	12.0 (3.31 – 43.2)	*<0.001*
Current smoker	12 (4.7)	5 (0.6)	7.83 (2.73 – 22.5)	
Exposed to second hand smoke at home				
No	145 (57.3)	443 (58.4)	1	
Yes	102 (40.3)	310 (40.8)	0.99 (0.74 – 1.33)	*0.13*
Missing	6 (2.4)	6 (0.8)		

Antenatal care during pregnancy				
Yes	27 (10.7)	402 (52.9)	1	
No	226 (89.3)	357 (47.1)	9.42 (6.16 – 14.39)	*<0.001*
Arsenic in drinking water				
Yes	11 (4.5)	29 (3.8)	1	
No	203 (80.2)	424 (55.9)	1.26 (0.61 – 2.57)	*<0.001*
Don't know	34 (13.4)	302 (39.8)	0.29 (0.14 – 0.65)	
Missing	5 (1.9)	4 (0.5)		
Place of delivery				
Hospital	9 (3.6)	59 (7.8)	1	
Home	242 (95.6)	699 (92.1)	2.26 (1.10 – 4.64)	*0.02*
Missing	2 (0.8)	1 (0.1)		

Table 2: *Association between smokeless tobacco consumption and stillbirth*

Variables	Frequency (n = 998)	Adjusted Odds Ratio (95% CI)*
STC Exposure, *n (%)*		
No	948 (94.9)	1
Yes	50 (5.1)	2.87 (1.36 – 6.08)
1- 5 times daily	29 (2.9)	1.67 (0.65 – 4.29)
> 5 times daily	21 (2.0)	5.89 (1.70 – 20.32)
		P[1] for tend <0.001

*Adjusted for participant's education, household income, age at 1st pregnancy, vaccination during pregnancy, complications during pregnancy, arsenic in drinking water, place of delivery and antenatal care during pregnancy. [1] for linear trend obtained from multiple logistic regression.