

ASSOCIATION BETWEEN PROLONGED MATERNAL SMOKELESS TOBACCO USE AND PREGNANCY OUTCOME

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Abstract:

About one third of the adults in the world including increasing number of women (250 million) daily smoke (22% in developed world & 9% of women in developing world). Approximately 28% women in Bangladesh use smokeless tobacco (ST). The incidence of adverse pregnancy outcome including spontaneous abortion, stillbirth, preterm delivery and giving birth to low birth weight baby (LBW) are quite high in Bangladesh. Tobacco is a preventable cause of maternal and neonatal mortality. This review article intended to find out any association between prolonged maternal smokeless tobacco use and pregnancy outcome. We reviewed various national & international research papers, thesis papers and articles about smokeless tobacco use and pregnancy outcome. It can be concluded that prolonged use of smokeless tobacco have significant association and risk with spontaneous abortion, stillbirth, preterm delivery and LBW baby.

Key words: Maternal use of ST, Pregnancy outcome, Smokeless tobacco.

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Introduction:

Tobacco is being used as smoking tobacco and smokeless tobacco (ST). Smoking tobacco is manufactured as cigarettes, bidis, cigars, kreteks, pipes and sticks. Smokeless tobaccos are: chewing tobacco, gul, moist snuff and dry snuff¹. About one third of the adults in the world including increasing number of women (250 million) daily smokes (22% in developed world & 9% of women in developing world)¹.

In Bangladesh commonly used smokeless tobaccos are: shada, jorda and gul. These are taken usually with betel quid, areca nut and lime and use of smokeless tobacco mixed with areca nut is very popular here. In Bangladesh smoking prevalence is 45% among men and 1.5% among women where 26% of men and 28% of women use smokeless tobacco in chewing form².

Tobacco is a priority health problem worldwide and currently it is the second major cause of death in the world. The World Health Organization estimates that smoking now

causes three million deaths annually and within two decades will cause more deaths than any single disease³.

History of tobacco: Cultivation of tobacco plant probably dates back 8000 years when two species of the plant, *N. rustica* and *N. tabacum*, were dispersed by American Indians through the Southern and Northern American Continent.

When Columbus landed in the New World in 1492, he was offered golden tobacco leaves as a courtesy. Within 150 years of his finding strange leaves, tobacco was being used around the globe. Its rapid spread through the Europeans¹ and widespread acceptance characterize the addiction to the plant *N. tabacum*.

Types of Tobacco use:

Now a day, tobacco is being used in various forms. The predominant use of tobacco can be broadly divided into smoking tobacco and smokeless tobacco.

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Smoking Tobacco:

The most widely prevalent and most studied form of tobacco use globally is cigarette smoking. Tobacco smoking has been in vogue for hundreds of years. With the spread of tobacco to Europe and other parts of the world from the 16th century tobacco smoking soon gained popularity.

Types of smoking tobacco: Tobacco can be smoked in a wide variety of ways. Various forms of smoking tobacco includes⁴: Cigarettes, Bidis, Cigers, Cheroots, Chuttas, Dhumti, Pipe, Kreteks, Sticks, Hooklis, Chillum, Hookah, Roll-your-own etc.

Health risks of smoking: Smoking harms nearly every organ of the body, causing many diseases and reducing the health of smoker in general. The common and well established health risks of smoking are summarized below^{1,4,5,6}.

Cancers - Lung cancer, oral cavity & pharyngeal cancer, laryngeal cancer, esophageal cancer, pancreatic cancer, bladder & kidney cancer, cervical & endometrial cancer, acute myeloid leukemia.

Cardiovascular diseases - Sub-clinical atherosclerosis, coronary heart disease.

Respiratory diseases - Chronic bronchitis & emphysema, asthma related symptoms.

Gastro-intestinal diseases - Stomach & duodenal ulcers.

Male reproduction- Sperm: deformity,infertility, impotence.

Female reproduction - earlier menopause, infertility & delay in conception.

Pregnancy outcomes - Spontaneous abortion, ectopic pregnancy, abruptio placenta, premature rupture of membranes, preterm birth, stillbirth, small for gestational age.

Eye diseases—Nuclear cataract, macular degeneration.

Bone & Teeth diseases- Osteoporosis in post menopausal women.

Smokeless Tobacco:

The term smokeless tobacco (ST) is used to describe tobacco that is consumed without

heating or burning at the time of use. The use of tobacco in various smokeless forms is very common in India, Bangladesh, Nepal and Myanmar. The different methods of consumption of ST include chewing, sucking, inhalation and applying tobacco preparation to the teeth and gum^{4,7,8}.

Types of smokeless tobacco:

Paan (betel quid) with tobacco: Paan consists of betel leaf, areca nut and slaked lime. In Bangladesh, sun dried tobacco is known as 'Shada'.

Jorda: Jorda is prepared by cutting tobacco leaves into small pieces and boiling them in water with slaked lime and spices until the water evaporates. It is then dried, and colouring and flavouring agents are added. Jorda may be chewed by itself, with areca nut or in betel quid .

Gul: It is a pyrolysed tobacco product. It is marketed in small tin cans and used as a dentifrice.

Snuff: Snuff consists of finely cut or powdered and flavored tobacco. It is of two types: moist snuff and dry snuff. Moist snuff is held in the mouth between cheek and gum. Dry snuff is inhaled through the nose.

Other forms of smokeless tobacco are: Chewing tobacco, Paan masala, Qiwam(Kiwam), Mainpuri tobacco, Hnatsay (Honey Soaked Tobacco), Mawa, Dohra, Tobacco and slaked lime (khaini), Gutka, Red Tooth Powder, Mishri (masheri or misheri), Creamy snuff, Gudhaku,Tuibur / Hidakphu, Tobacco Water, Gundhaku, Bajjar and Creamy snuff.

Pharmacology of smokeless tobacco: ST contains more than 2500 chemical constituents⁷. Among the chemical constituents nicotine is of particular concern. It is a tertiary amine composed of pyridine and pyrrolidine ring. In its non-ionized form, nicotine freely permeates through the membranes, including the buccal mucosa and blood brain barrier. Nicotine is absorbed more slowly from ST than from tobacco smoke but peak venous levels are similar. The systemic absorption of nicotine is greater with the use of chewing tobacco or snuff compared with that from

smoking cigarettes. Nicotine is extensively metabolized by the liver. The major metabolite is cotinine.

Health risks of smokeless tobacco

The potential adverse health consequences of ST are: Nicotine dependence, accelerated coronary & peripheral vascular disease, stroke, hypertension, delayed wound healing, reproductive disorders (LBW, prematurity, spontaneous abortion, stillbirth, increase in male fetal wastage, increase in placental weight), peptic ulcer disease, esophageal reflux, dental carries, oral leukoplakia and oral, oropharyngeal, laryngeal & esophageal cancers^{9,10,11}.

Pathophysiology

The precise mechanism by which tobacco causes adverse pregnancy outcome is not completely understood. Placental and biochemical factors in pregnant women have been considered, and the influence of chemicals in tobacco has been studied.

Smokeless tobacco and smoking both have been associated with abnormal placental pathology.

ST users are exposed to higher level of nicotine than smokers. The systemic absorption of nicotine per dose is greater with use of chewing tobacco (average 4.5 mg from average dose of 7.9g chewed over 30 minutes) or snuff (average 3.6mg from an average 2.5g moist snuff kept in mouth for 30 minutes, compared with that from smoking cigarettes (average 1mg/cigarette)⁹. Nicotine of ST may cause same adverse pregnancy outcome as smoking.

Nicotine is a strong vasoconstrictor. It constricts the uterine artery and umbilical artery and thus reduces the blood flow to the fetus. It increases maternal blood pressure and heart rate. An increase in fetal heart rate is also seen, which is thought to be caused by fetal hypoxia¹². Nicotine is also associated with significant decrease of most amino acids in both placental tissue and fetal plasma¹³. Nicotine also alters the peripheral autonomic pathways, leading to increased susceptibility to hypoxia induced brain damage and perinatal mortality¹⁴.

Pregnancy Outcome

Pregnancy outcome may be defined as results of conception and ensuing pregnancy, including live birth, stillbirth and abortion.¹⁵ Normal pregnancy outcome is term normal weight (2500gm to 4000gm) newborn without any congenital anomaly.

Adverse pregnancy outcomes may be: Abortion-Spontaneous & induced, stillbirth, preterm birth, LBW baby and IUGR.

Tobacco and Spontaneous Abortion

It is difficult to evaluate the effects of maternal smoking on miscarriage, primarily because of inherent difficulty in measuring the general population's rate of spontaneous abortion. Many studies were done to measure the relationship between smoking and spontaneous abortion.

Ness RB et al.¹⁶ studied the association between cocaine & tobacco use and spontaneous abortion among 970 pregnant adolescents and women. A total of 400 adolescent and women had spontaneous abortion. Among them 34.6% smoked on the basis of urine cotinine assay. The presence of cotinine in urine was independently associated with an increased risk of spontaneous abortion (odd's ratio 1 .8; 95 percent confidence interval, 1.3 - 2.6).

Gayle CW et al.¹⁷ examined the risk of spontaneous abortion from environmental tobacco smoke exposure in a prospective study over 5,000 women in California during 1990-1991. Among non-smokers there was little association by hours of ETS exposure at home or at work. A moderate association with maternal smoking was observed (adjusted odd ratio for < 5 cigarettes per day, 1 .3).

Walsh RA¹⁸ reviewed many studies and summarized that substantial non-experimental evidence indicates that smoking causes spontaneous abortion. The relative risk of spontaneous abortion in smokers is increased by over one-third after controlling for confounding factors. The positive association between smoking and spontaneous abortion has been found over 80% of studies, and the data also convincingly demonstrate a dose-

response gradient based on daily cigarette consumption during pregnancy.

In Bangladesh Hoque M, Rahman ME¹⁹ showed spontaneous abortion was higher in ST user group (odds ratio 2.3 and $p < 0.01$) and in India Krishnamurthy S²⁰ showed similar association (30% male foetal wastages due to tobacco use).

Tobacco and stillbirth

Smoking has repeatedly been associated with stillbirth, and the risk generally increases with the amount smoked.

In Bangladesh Hoque M, Rahman ME¹⁹ showed stillbirth was higher in ST user group (odd ratio 2.0 and $p < 0.01$) than non ST user group.

Raymond EG et al.²¹ conducted a population based cohort study in Sweden between 1983 and 1989 to examine the effects of advanced maternal age, parity and smoking on risk of stillbirth. A total of 6,38,242 pregnancies were studied. The study revealed increased stillbirth risk in smokers.

Cnattingius et al.²² examined the risk factors for late fetal death and early neonatal mortality in a population based prospective study. All Swedish births between 1983 and 1985, 281808 births were included. The overall rate of late fetal death was 3.5. About 30% of the pregnant women were recorded as being smokers. Logistic regression analysis showed significant relative risk for late fetal death and maternal smoking.

Dodds et al.²³ conducted a case control study in Canada between 1999 and 2001. The study included 105 stillbirth cases and 389 live-birth controls. The study found that smoking during first trimester of pregnancy was associated with increased risk of stillbirth (adjusted hazard ratio 2.4; 95% CI, 1.2-4.9).

A prospective cohort study in Mumbai, India by Gupta PC, Sreevidya S²⁴ found the risk for stillbirth in ST users was 2.6 times than non users.

Krishnamurthy S showed that maternal ST ingestion causes delivery of LBW baby 3.2 times and still birth 3 times than non ingested mothers²⁵.

Tobacco and Preterm Birth

Many studies have reported that smoking is associated with preterm labor. A dose response relationship of cigarette smoking and premature delivery was also documented.

A study done in Bangladesh by Hoque M, Rahman ME¹⁹ showed preterm delivery was higher in ST user group (odd ratio 3.1 and $p < 0.01$).

England U et al.²⁶ examined birth weight, preterm birth and pre-eclampsia in women who delivered singleton live born infants in Sweden from 1999 through 2000. After exclusion 789 snuff users, 11240 smokers and 11,495 non-users remained. Compared with non-users, preterm delivery was increased in snuff users and smokers (adjusted odd ratio 1.98 and 1.57 respectively).

Kallen K²⁷ studied 1,413,811 infants born between 1983 and 1996 in Sweden. The study found significant association between maternal smoking and preterm birth. The odd ratios for maternal smoking (>10 cigarettes per day and ≥ 10 cigarettes per day) and preterm delivery were 1.39 and 1.65 respectively (dose response $P < 0.001$).

McDonald AD et al.²⁸ analyzed data from an occupational and other factors in pregnancy to assess the effects of cigarette, alcohol and coffee consumption on pregnancy outcome. A total of 51512 pregnancies were studied. Smoking accounted for 11% of preterm births. Prematurity was higher among smokers than non-smokers and increased with number of cigarette smoked.

Another study done in Bangladesh by Hossain MA, Rahman ME²⁹ found that maternal ST use in pregnancy was significantly associated with preterm delivery and carries a risk of having preterm babies 4.6 times than non-ST users.

The prospective cohort study in India by Gupta PC, Sreevidya S³⁰ found that risk of preterm delivery was 1.4 times higher for women who used ST than non user.

Tobacco and LBW

The most recognized effect of maternal smoking is the increased risk LBW baby. In addition to

preterm delivery tobacco, both in smoking and smokeless form, is associated with IUGR.

Krishnomurthy S and Joshi S²⁵ studied 178 singleton live births to see the effects of maternal smokeless tobacco use in pregnancy. The authors found that maternal use of 'Mishri' tobacco in pregnancy was associated with LBW baby (3.2 times more risk of having a LBW baby).

A prospective cohort study done in Mumbai, India by Gupta PC, Sreevidya S³⁰ showed that there was 1.6 times more risk of LBW for women who used ST than non users.

Steyn et al.³¹ found that the mean birth weight for non-tobacco users was 3148 gm and that of the smokers 2982 gm, resulting in a significant lower birth of 165 gm for babies of smoking mothers (P =0.005). In contrast women using snuff gave birth to infants with a mean birth weight of 3118 gm which is a non-significant decrease (p=0.52) in their infants birth weight compared with those not using tobacco.

Wang X et al.³² conducted a cohort study including 740 white and Hispanic women between 1986 and 1992. This study examined the relationship of birth outcomes to the timing and intensity of maternal active and passive smoking estimated both from self report and from cotinine concentration in maternal urine during early, middle and late gestation. A significant inverse exposure-response relationship between cotinine concentration in urine and infant's size at birth was demonstrated.

More studies done in Bangladesh^{19,33,34} showed there was 4.1 times, 2 times and 2.2 times respectively more risk of LBW for women who was used ST than non users.

Deshmukh JS et al.³⁵ studied the prevalence of LBW and its association with maternal factors in India. They found tobacco exposure (both smoking and smokeless tobacco) was significantly associated with LBW baby (odd ratio 3.14).

Prevention:

Tobacco is a preventable cause of adverse pregnancy outcome. So, we should make all the possible efforts to prevent these tobacco related adverse pregnancy outcomes.

Smoking and Tobacco Product Usage (Control) Act 2005

Bangladesh has enacted a tobacco control law in 2005 in accordance with some of the provisions of WHO Framework Convention on Tobacco Control (FCTC).

According to this law 'Tobacco Products' means any product made from Tobacco which can be inhaled through smoking and shall include bidi, cigarette, cherrot, cigar and mixtures used as pipe.

It is noteworthy that the definition of tobacco products does not include Smokeless Tobacco. So, the act should be revised to control use of smokeless tobacco.

Nicotine Replacement Therapy

Intervention to quit tobacco includes behavior therapy and pharmacotherapy. The only drug treatment readily available for quitting tobacco use is nicotine replacement therapy. Currently available drugs are Nicotine gum, transdermal nicotine patch, nicotine aerosols, Bupropion SR, Zyban.

Nicotine vaccine:

Researches for human nicotine vaccine are going on. In near future, it may be possible to use nicotine vaccine to protect the fetus from the detrimental effects of maternal tobacco use.

NicVAX³⁶ is a nicotine conjugate vaccine intended to reduce or eliminate physical addiction to nicotine. According to National Institute of Drug Abuse, NicVAX can potentially be used to inoculate against addiction. This proprietary vaccine is being developed by Nabi Biopharmaceuticals. NicVAX consists of the hapten 3'-aminornethylnicotine which has been conjugated to *Pseudomonas aeruginosa* exoprotein.

The vaccine is designed to cause the immune system to produce antibodies that bind to nicotine and prevent it from entering the brain. NicVAX is still under development; it is currently on phase III of testing.

Conclusion:

Public awareness about the adverse pregnancy outcome of tobacco use should be increased,

using all possible channels of communication of mass education as well as for influencing women. Women & female children should be discouraged to take and to be habituated to smoking & ST. Women who are already habituated to smoking or any other tobacco product should be advised to quit this habit before being pregnant and during pregnancy. Women should be helped who are willing to quit tobacco. There should be restriction about the advertising and promotion of tobacco products.

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