

## Review Article

# Tobacco use in Pregnancy- Global evidence and Relevance to LMIC

Pratima Murthy\* and Shree Mishra

*Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), India*

## \*Corresponding author

Pratima Murthy, Department of Psychiatry, National Institute of Mental Health and Neuro Sciences, Bangalore 560029, India, Tel: 919844094482; Email: pratimamurthy@gmail.com

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## Abstract

While smoking prevalence is showing a decline in high income countries (HIC), smoking among pregnant women has also reduced and current prevalence in certain HIC is between 8.4 to 11.4%. In low and middle-income countries (LMIC), exposure to second-hand smoke (SHS) and the use of smokeless tobacco (SLT) are significant problems. While pooled prevalence of smokeless tobacco use across 54 LMIC's was 2.6%, several countries particularly in the south Asian and West Pacific region show tobacco use prevalence higher than the pooled prevalence and rates of SLT use among pregnant women in Nepal, Bangladesh and India are 22%, 20% and 15% respectively. In many countries, pregnant women face high rates of exposure to SHS. Maternal smoking is associated with several adverse consequences for both mother and child. While a range of adverse fetal outcomes have been described, the strongest causal effects are for ectopic pregnancy and orofacial clefts. With SLT use, pre-term and small for gestation have been consistently demonstrated. Meta-analytical studies support the effectiveness of psychosocial interventions for smoking cessation. The same cannot be said of smokeless tobacco use among pregnant women in LMIC. Poverty, illiteracy, use of tobacco in the partner, poor motivation to quit, stigma are some of the common barriers to treatment in all settings, and decision not to breast-feed has been shown to be associated with a greater likelihood of relapse. There is no supporting evidence for pharmacotherapy for tobacco cessation in pregnancy and there is a growing concern of the use of E-cigarettes by pregnant women under the perceived notion that they are safer. Approaches to cessation, in addition to providing individual support, must also focus on evidence-based population strategies to reduce tobacco consumption. Asking for tobacco use and tobacco exposure, objective documentation and support to quit and to reduce SHS exposure must be offered in all maternity settings.

## ABBREVIATIONS

LMIC: Low and Middle Income Countries; HIC: High Income Countries; SHS: Second Hand Smoking; SLT: Smokeless Tobacco; NRT- Nicotine Replacement Therapy

## INTRODUCTION

Tobacco use in any form has been a growing concern worldwide. It is the 'only legal drug that kills many of its users, when used as it is intended'. The tobacco epidemic is one of the biggest public health threats the world has ever faced, killing more than 7 million people each year [1]. Nearly 80% of the world's more than 1 billion smokers live in low and middle-income countries. These countries, in addition to smoking, have a large burden of smokeless tobacco use, with nearly 90% of global smokeless tobacco users living in the South-East Asia region [2]. Second-hand smoking is attributable to 1% of deaths world-wide with 47% of these deaths occur in women and 28% in children [3].

Smoking in developed countries like the United States has shown an overall decline from 20.9% in 2005, to 15.1% in 2015 [4]. While smoking prevalence in younger age group females in the United States has been stabilizing, 17% of high school females report tobacco use [5]. However, smoking prevalence is of significant concern in developing countries like India [6]. While more men than women across the world are likely to be smokers, the prevalence of smoking among younger girls is high compared to adult females [7]. Smokeless tobacco use among women is most commonly reported from South-East Asia, with a relatively high prevalence in Bangladesh (27.9%) and India (18.2%) [8].

## EPIDEMIOLOGY OF TOBACCO USE IN PREGNANCY

Tobacco in any form, either active or passively delivered brings has been associated with many adverse pregnancy-related outcomes. This selective review examines the prevalence of tobacco use (smoking and smokeless forms) during pregnancy, the risks from exposure to smoking (both through active smoking

and exposure to second-hand smoke) and smokeless tobacco use during pregnancy.

Although many of the high income countries have shown remarkable reductions in the prevalence of smoking among pregnant women, this continues to be a source of concern, with a prevalence of 8.4% in the United States [9], 11.4 % in the UK [10], and 11% in Australia [11]. From the Demographic and Health Surveys (DHS), done in 54 LMICs between 2001 and 2012, comprising 58922 pregnant women (aged 15-49), the pooled prevalence of any tobacco use in pregnant women in LMICs was calculated at 2.6%(95% CI 1.8-3.6). The South-East Asian region had the highest pooled prevalence at 5.1% (1.3-10.9) [12]. Countries which had prevalence higher than the pooled prevalence included Cambodia and Philippines in the West Pacific (6.7% and 2.5% respectively; four in South-East Asia [Nepal (8.4%), India (8.0%), Timor-Leste (3.7%), Maldives (3.4%)]. The 2008-10 Global Adult Tobacco Survey of 14 LMICs showed that in women of reproductive age, prevalence of current tobacco smoking ranged from 0.4% in Egypt to 30.8% in Russia [12].

## SMOKELESS TOBACCO USE DURING PREGNANCY

While the pooled prevalence of current smokeless tobacco use was less than 1% in most countries, it is common in Bangladesh (20%), India (15%) [12,13], and in Nepal (22%) [14]. Studies in India have consistently found a high prevalence of smokeless tobacco use among pregnant women, with as many as 64% from an urban slum reporting SLT use [15].

## SECOND-HAND SMOKING EXPOSURE

A study from Argentina interviewed women attending one of 21 clusters of publicly-funded prenatal care clinics regarding SHS exposure during pregnancy at the time of their hospitalization for delivery during 2011-2012. More than a third (35.9 %) of women were exposed to SHS at home or work [16]. Another study from Greece reported that while the prevalence of active smoking during pregnancy was 36%, 94% of the women studied were exposed to SHS, with 72% of the women exposed at home and 64% of them in a public place [17]. A review from China indicates that 38.9% to 75.1% pregnant women were exposed to second-hand smoking [18].

## RISKS OF SMOKING AND SMOKELESS TOBACCO IN PREGNANCY

Since the first concern of the risks of tobacco use in pregnancy in 1935 [19], there has been growing evidence of the harms from tobacco use in pregnancy.

One of the effects attributed to tobacco use is its impact on the ability to become pregnant. Studies have indicated reduced fertility and fecundity in female smokers and lesser chances of ability to conceive during IVF. The reduction in fertility has been seen in grown up individuals who were exposed to tobacco smoke in utero reflecting an intricate and complex mechanism affecting conception [20].

Many studies have reported an association of maternal tobacco smoke exposure with a variety of adverse mother and child outcomes. These associations are summarized in Table 1.

## ADVERSE MATERNAL OUTCOMES

Studies have demonstrated adverse cardio-vascular outcomes with smoking in women in general [62], and these effects are likely to get aggravated in pregnancy. In addition to hypertension and increased risk of cardiac disease, an increased risk for gestational diabetes has also been described in pregnant smokers [28].

### Placental abnormalities

A range of placental abnormalities have been described [63]. Changes in placental blood flow and an altered balance between proliferation and differentiation of the cytotrophoblast has been observed, reflecting changes in gene and protein expression in the cytotrophoblast. Smoking in pregnancy has been linked with thickening of the trophoblastic basement membrane, increased collagen in the villous mesenchyme and decreased vascularization of the placenta. Cadmium in smoke has been found to cause complex enzymatic changes leading to IUGR.

### Adverse fetal outcomes

Even in HMIC settings, it is suggested that maternal smoking could contribute to 20% of the still births [29]. In a large meta-analysis of 172 articles pooling 173687 children with congenital abnormalities compared with 11674332 unaffected controls, increased risk of congenital abnormalities was demonstrated for a variety of conditions [39]. A variety of health related adverse outcomes in both infants and older children have been described. These include neurobehavioral outcomes including attention deficit hyperactivity disorder, aggression and depression.

Second hand smoking is also linked with reduced birth weight (30-40gm, OR ranging from 1.2 to 1.25), SIDS, preterm birth as well as childhood cancers [64].

As tobacco smoke contains several carcinogens which cross the placental barrier, it is plausible that there would be an increased risk of cancer in the offspring. Both genotoxic effects and the creation of a tumor-supporting microenvironment by nicotine have been observed in vitro and in animal studies [65]. A meta-analysis examining the risk of leukemias and brain tumors among children exposed to ante-natal smoking found an increased risk for brain tumors but not for leukemias. Another recent review from the Danish national registers [66], did not find a positive association with maternal smoking and childhood cancers.

With increasing rates of obesity and diabetes and survival of preterm infants born at early gestational ages, the need to elucidate mechanisms responsible for programming of adult cardiovascular disease is essential for the treatment of upcoming generations [67].

While the above associations have been reported from many studies, according to the Surgeon-General's report from the USDHHS 2014, [68], a causal evidence between maternal smoking and adverse reproductive outcomes can be definitely established for the following risks- ectopic pregnancy and congenital malformations including orofacial clefts. Other adverse outcomes are surmised as being suggestive. This report also suggests that the evidence is insufficient to infer the presence or absence of

**Table 1:** Adverse maternal and fetal consequences of maternal smoking.

<b>Risks associated with smoking for mother</b> [17,21-27]
Pregnancy-induced hypertension
Ectopic pregnancy
Abortion
Pre-term delivery less than 37 weeks
Pre-eclampsia
Abruptio placenta
Placenta previa
Post-partum haemorrhage
Gestational diabetes [28]
<b>Adverse fetal outcomes associated with exposure to tobacco smoke in utero</b>
Stillbirth [29,30]
Premature birth [31,32]
Intrauterine growth retardation [26,33]
Small for gestational age (SGA) [26,33-37]
Increased perinatal mortality Sudden infant death syndrome (SIDS) [26,33,37,38]
Congenital Defects [39]
Cardiovascular/heart defects [OR 1.09, 95% confidence interval (CI) 1.02-1.17];
Musculoskeletal defects (OR 1.16, 95% CI 1.05-1.27);
Limb reduction defects (OR 1.26, 95% CI 1.15-1.39);
Missing/extra digits (OR 1.18, 95% CI 0.99-1.41);
Clubfoot (OR 1.28, 95% CI 1.10-1.47);
Craniosynostosis (OR 1.33, 95% CI 1.03-1.73);
Facial defects (OR 1.19, 95% CI 1.06-1.35);
Eye defects (OR 1.25, 95% CI 1.11-1.40);
Orofacial clefts (OR 1.28, 95% CI 1.20-1.36);
Gastrointestinal defects (OR 1.27, 95% CI 1.18-1.36);
Gastroschisis (OR 1.50, 95% CI 1.28-1.76);
Anal atresia (OR 1.20, 95% CI 1.06-1.36);
Hernia (OR 1.40, 95% CI 1.23-1.59); and
Undescended testes (OR 1.13, 95% CI 1.02-1.25).
Obesity in the infant [40]
Childhood Asthma [41,42]
Lung infections [31,43-45]
Dental caries [46]
Otitis media [47]
Chron's disease [48]
Older children (health effects) [49]
Depression and anxiety [50]
ADHD and other neurobehavioral symptoms [51-53]
Academic problems [54]
Adolescent bone health [55]
Early onset type-2 diabetes and non-diabetic obesity [28]
Childhood cancers [56]

a causal relationship between maternal prenatal smoking and the following disorders in the offspring- anxiety, depression, Tourette's syndrome, schizophrenia and intellectual disability.

## SMOKELESS TOBACCO USE BY PREGNANT WOMEN- ADVERSE CONSEQUENCES

Smokeless tobacco causes a whole host of adverse consequences, which are outside the scope of this review. These consequences are also relevant to the pregnant woman, in addition to the specific associations mentioned in Table 2. With respect to adverse fetal outcomes, a systematic review of 9 studies with diverse methodology reported significant associations with SLT use in 5/7 studies for LBW, in 3/6 studies for preterm, in all 4 studies for stillbirth and in 1/2 studies assessing SGA [61]. Many

Indian studies have also consistently demonstrated adverse fetal outcomes [60] (Table 2).

## ETIOLOGY OF TOBACCO RELATED ADVERSE HEALTH OUTCOMES

Nicotine itself is a neuroteratogen affecting many important milestones in brain development, often causing long term cognitive, behavioral, emotional sequelae and even addictive behavior in the offspring exposed to tobacco during pregnancy. It is also noted to affect development of many organs, especially the lungs [69].

Carbon monoxide in tobacco smoke is clearly fetotoxic and results in fetal hypoxia in chronic exposure and fetal death in acute exposure. There are many carcinogens in tobacco smoke which have been shown to be toxic in animal fetus, needs further research in humans [70].

## AMOUNT OF EXPOSURE

Although no level of tobacco use is safe during pregnancy, greater smoking intensity has been shown to be associated with greater deleterious effects on the fetus [71].

## OTHER CO-MORBIDITIES

While addressing issues related to tobacco use in pregnancy, it is important to be aware that pregnant mothers may also be exposed to alcohol, cannabis and other drugs which may also contribute to adverse fetal outcomes [72,73].

## ADDRESSING TOBACCO USE IN PREGNANCY

Most tobacco intervention programs in pregnancy have focused on smoking tobacco.

All intervention starts with a comprehensive assessment. The 4A's- "ask, advice, assess, assist, and arrange" is recommended by the National Cancer Institute for counselling smokers in clinical practice and also by the Agency for Health Care Policy and Research (AHRP) [74].

Approaches have included behavioral support delivered in a variety of settings and formats, self-help interventions, and measures of effectiveness have included both validated measures like breath CO levels, as well as urinary cotinine measures, in

**Table 2:** Adverse maternal and fetal consequences of maternal smokeless tobacco use.

<b>Risks associated with smokeless tobacco use for mother</b>
Studies from LMIC [57-60]
Maternal anemia
Underweight mothers
Pregnancy induced hypertension
Ante-partum haemorrhage
Oligohydramnios
Polyhydramnios
Post-partum haemorrhage
<b>Adverse fetal outcomes associated with smokeless tobacco use during pregnancy</b>
Still birth (HRadj)= 2.6 [58]
Fetal distress (RR=1.8 (1.06-3.06)
Low birth weight [57,59]
Pre-term births
Small for gestational age (SGA) [61]

addition to self-report [75]. This is important as self-reporting of tobacco use can be biased on many occasions related to its potential of perceived stigma by the pregnant respondent. [76].

A study examining predictors of relapse found that non-intention to quit, lower quitting confidence, the presence of other household smokers and not planning to breast feed were short-term (1 month) predictors of relapse and low motivation to quit, a smoking partner were predictors of relapse at 12 months [76].

Pooled results of 72 trials, including 56 randomized control trials of more than 20,000 pregnant women (Cochrane databases) show that cessation interventions reduce smoking in late pregnancy [IR 0.94, 95% CI 0.93 to 0.96] and reduce incidence of low birth weight [RR 0.83, 95% CI 0.73 to 0.95] and pre-term births [RR 0.86, 95% CI 0.74 to 0.98] while increasing birth weight by a mean of 53.91g [95% CI 10.44g to 95.38g]. There were no statistically significant differences in neonatal intensive care unit admissions, very low birthweight, stillbirths, perinatal or neonatal mortality but these analyses had very limited power [77]. Some of the earlier reviews found no evidence that more intensive interventions work any better than brief interventions [75].

A recent review [78], included 102 randomised controlled trials with 120 intervention arms (studies) and data from 88 randomised controlled trials (involving over 28,000 women). The main intervention strategies were categorised as counselling (n = 54), health education (n = 12), feedback (n = 6), incentives (n = 13), social support (n = 7) and exercise (n = 1). This review provided moderate- to-high quality evidence that psychosocial interventions increased the proportion of women who had stopped smoking in late pregnancy by 35%, mean infant birthweight (by 56 g), reduced the number of babies born with low birthweight (by 17%) and admitted to neonatal intensive care immediately after birth (by 22%). A greater effect size was observed for incentive-based interventions. However, these studies were mostly from HICs. Counselling interventions had a clear effect on stopping smoking compared with providing usual care (from 30 studies), and a smaller effect when compared with less intensive interventions (18 studies), which was at variance with other reviews [78].

Programs in HIC addressing the issue of smoking during pregnancy have been present for more than two decades. Rates of smoking in pregnancy have significantly fallen in these countries, but smoking rates among indigenous women continue to be high because of socioeconomic disadvantage, social norms, and poor access to culturally appropriate tobacco cessation support [79].

More recently, a study from Australia which found a decline in the prevalence of smoking during pregnancy in NSW between 2003 and 2011 concludes that this decline was not a direct result of the antismoking activities evaluated, but to the wider tobacco control policies [80].

## PHARMACOTHERAPY FOR TOBACCO CESSATION IN PREGNANCY

While the available evidence suggests no major benefit of nicotine replacement therapy. (NRT) in smoking cessation in pregnant populations, it has been suggested that NRT would

be less harmful as compared to the other chemicals in active smoking. However, there are also preliminary studies that suggest increased fetal malformation with NRT[70].

An observational study has suggested combination NRT may be more effective than single form NRT (patch or rapid acting form) in pregnant women [81]. This finding may be related to faster metabolism of nicotine in pregnancy. Other first line drugs like bupropion and varenicline are not recommended in pregnant populations due to the lack of RCTs and safety studies in this population [82,83].

## USE OF E-CIGARETTES

A study in 2014 predicted that the perceived safety of e-cigarettes may lead to e-smoking during pregnancy [84]. A recent online survey of 445 pregnant women recruited online, found that 5.6% of the women reported smoking cigarettes, 6.5% used only e-cigarettes and 8.5% used both tobacco cigarettes and e-cigarettes [85]. In this study, a majority of participants (64.3%) viewed e-cigarettes as being safer than tobacco cigarettes, and this perception was greatly influenced by having seen advertisement for e-cigarettes [85]. However, e-cigarettes are not recommended as a substitute for cigarette smoking cessation during pregnancy [86].

## CONCLUSION

Tobacco use in any form in pregnancy is associated with a plethora of adverse fetal effects as well as maternal risks. Existing effective interventions are primarily behavioral, but public health measures focused on tobacco control are also important in reducing risks from tobacco use during pregnancy. While there has been an encouraging reduction in the prevalence of smoking in HICs, exposure to SHS as well as smokeless tobacco use are serious problems globally, as well as in LMIC, particularly in South Asia. Identification of smoking and smokeless tobacco use, as well as exposure to second-hand smoking and interventions in such cases must become part of standard care in all maternity care settings.

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