Pregnancy Outcome in Occupational Tobacco Exposure: A Cohort Study from South India

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Abstract

Background: Women constitute a significant labor pool in the Indian tobacco industry as bidi rollers. On an average, they roll around 600 bidis/day and are exposed to 120 g of tobacco and 3 g of nicotine. Bidis do not have chemical preservatives or stabilizing agents, and therefore, the rollers are exposed only to nicotine by handling and inhalation. The study objective was to assess pregnancy outcome in these women with occupational tobacco exposure. Materials and Methods: A prospective cohort study of bidi-rollers (n = 177) and women with no tobacco exposure (n = 354), followed up for pregnancy outcome, neonatal anthropometry, and nicotine absorption by cotinine assays. Adjusted risk and adjusted mean differences with a 95% confidence interval were derived. Results: Outcomes included increased adjusted risk for gestational hypertension (3.54 [1.21, 10.31]; P = 0.021) and fetal growth restriction (2.71 [1.39, 5.29]; P = 0.004). Risk for prematurity was not statistically significant (1.81 [0.74, 4.45]; P = 0.194). Lower adjusted mean difference of birth weight (−104 g [−177, −31]; P = 0.005), length (−0.4 cm [−0.8, −0.1]; P = 0.006), and head circumference (−0.4 cm [−0.6, −0.1]; P = 0.002) were seen with increased risk for small gestational age (1.75 [1.12, 2.73]; P = 0.015). Nicotine absorption was evident in one-third of maternal and cord blood estimations. Conclusion: Occupational passive tobacco exposure results in adverse pregnancy outcome.

Keywords: Occupational passive tobacco exposure, nicotine, cotinine assay

INTRODUCTION

India is the world’s third-largest tobacco producer and the second-largest consumer. Bidi is a hand-rolled cigarette consisting of shredded and sun-dried tobacco (Nicotiana tabacum) dust wrapped in a tendu (Diospyros melanoxylon) leaf. Bidi rolling is a traditional, labor-intensive occupation in several states of India. Women constitute a significant labor pool as bidi rollers and work from home. A woman rolling around 600 bidis/day is exposed to 120 g of tobacco and 3 g of nicotine, it is natural alkaloid. Nicotine is an efficient skin penetrator because of its low-molecular-weight and high solubility. Skin serves as nicotine depot and rinsing with soap and water is only partially effective in its removal. Bidis do not have chemical preservatives or stabilizing agents, and therefore, the rollers are exposed only to nicotine by handling and inhalation.

Nicotine is concentrated by the placenta, and its level in the fetal circulation is 15% higher than the maternal circulation. It is also reabsorbed through the fetal skin and gastrointestinal tract from the amniotic fluid. Nicotine impacts the fetal outcome in several ways. It decreases the mitotic potential of trophoblasts and results in abnormal placentation in the early weeks of pregnancy. It also has vasoconstrictive effects on uterine and umbilical arteries. Chronic exposure increases vascular resistance in the uteroplacental circulation and disrupts villous establishment leading to fetal hypoxia. More recently, nicotine has been implicated in alterations of DNA methylation and gene expression related to fetal growth.

Adverse pregnancy outcome is established in maternal cigarette smoking and exhibits dose-exposure causality. Smoking

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exposes the mother–fetus dyad to nicotine, carbon monoxide, nitrosamines, and polycyclic aromatic hydrocarbons. Pooled odds ratio (OR) in the range of 1.2–2.4 has been noted for adverse outcomes, such as placental abruption, placenta previa, preterm premature rupture of membranes (PPROM), fetal growth restriction (FGR), prematurity, and low birthweight. A decrement of 200 g in mean birth weight is reported with active maternal smoking, and 10–100 g with environmental exposure to tobacco smoke, and 17–93 g with exposure through maternal snuff use or tobacco chewing.

Approximately 47% of newborns are born small for gestational age (SGA) in India. Very few Indian studies have assessed the effect of occupational tobacco exposure on newborn birthweight with contradictory results. Moreover, these studies are cross-sectional and have not addressed maternal outcomes. There are 0.25 million registered bidi rollers in the study region. This study was designed to assess pregnancy and birth outcomes in tobacco handlers. We also evaluated nicotine absorption in the mother–fetus dyad using serum cotinine assay. Cotinine, with a half-life of 16 h, is a well-established surrogate biomarker of nicotine exposure.

**Materials and Methods**

**Participant selection and research setting**

This was a hospital-based prospective cohort study. The study group consisted of women between the ages of 19 and 35 years with singleton pregnancies and having no antecedent chronic illnesses. They were enrolled between 18 and 22 weeks of gestation and followed at 26–28 weeks, 34–36 weeks, and at delivery. The study period was 36 months between May 2014 and April 2017. The study had the approval of the Institutional Ethics Committee. Informed written consents were obtained from the participating women.

**Exposure definition**

Exposure was defined as bidi rolling for at least 1 year before and continued into pregnancy. Exposed and unexposed cohorts were those with and without occupational tobacco exposure through bidi rolling, respectively. Exclusion criteria in both groups were as follows: (i) active exposure to tobacco through smoking or nonsmoking snuff inhalation and chewing tobacco and (ii) passive exposure (≥2 h to smoking at home or workplace) to tobacco. A serum cotinine value ≥2 ng/mL in the unexposed group at enrollment or delivery was considered nondisclosed exposure. Women with such values were excluded from the analysis.

**Data collection and definitions**

Women in the exposed group were interviewed at each antenatal visit regarding bidi rolling and handling practices. In addition to demographic data, the socioeconomic class was established using Kuppuswamy scale. Pregnancy was monitored for maternal weight gain, anemia, hypertension, gestational diabetes mellitus, and FGR. Other outcomes included abortions (≤20 weeks), intrauterine death, placental abruption, placenta previa, PPROM, and prematurity. The World Health Organization definitions were used to describe all pregnancy-related illnesses.

Maternal anemia was defined as hemoglobin <11 g/dL at any trimester. Hypertension was categorized as gestational hypertension or pregnancy-induced hypertension (preeclampsia). Gestational hypertension was defined as new-onset hypertension at ≥20 weeks gestation, with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on two occasions, 4 h apart. Preeclampsia was diagnosed in the presence of proteinuria ≥1+ or end-organ dysfunction. Gestational diabetes mellitus was diagnosed based on the second-trimester one-step screening with 75 g oral glucose tolerance test (fasting sugar >92 mg/dL). FGR was defined as a fetus with estimated weight <10th centile for gestational age (GA) and deceleration of growth in serial sonograms done at a 3–4-week interval.

Data on live births included GA in weeks, maturity, and growth parameters. GA was based either on maternal last menstrual period or new Ballard scoring when there was ≥2 weeks discrepancy on sonogram. Term birth was defined as GA 37 and 42 weeks and preterm <37 completed weeks. Preterm births were further divided into very preterm (28–31 completed weeks), moderate preterm (32–36 completed weeks), and late preterm (34–36 completed weeks). Birthweight was recorded to the nearest gram (g) using a calibrated electronic weighing scale, length was measured in centimeters (cm) using an infantometer, and head circumference was measured in cm using a nonstretchable measuring tape. Neonates were classified as appropriate for GA if their birth weights ranged between 10th and 90th centiles, SGA if <10th centile or large for GA if >90th centile when plotted on the intrauterine growth curves.

Maternal cotinine assays were performed at 18–22 weeks and delivery in both groups. Umbilical cord blood cotinine assay was performed in the exposed group. Serum was separated and stored at −80°C until analysis. Cotinine assays were carried out by commercial solid-phase competitive ELISA (Calbiotech, USA) and expressed as ng/mL. A serum cotinine value ≥2 ng/mL was considered indicative of nicotine absorption.

**Outcome measures**

Primary outcomes were pregnancy-related complications, FGR, prematurity, and newborn anthropometry in the exposed and unexposed groups. The secondary outcome was nicotine absorption as determined by serum and cord blood cotinine assays in the exposed group.

**Sample size and matching**

We used open-source calculator, OpenEpi, Version 3 (OpenSource.org, USA) for sample size estimation (https://www.openepi.com/SampleSize/SSCohort.htm). Calculation was based on the following: two-sided significance (1-alpha) of 95%, power of 80%, ratio of unexposed/exposed of 2:1,
percentages of unexposed and exposed with SGA in 20% and 30%, respectively, and an anticipated OR of 1.8 for SGA in the exposed. With this, the sample size required was 175 in the exposed group and 350 in the unexposed group. Selection bias was minimized by matching the exposed and unexposed groups for parity and socioeconomic class. Additional participants were enrolled to offset anticipated 2%–5% dropout.

Analysis
Statistical analysis was performed using the software SPSS version 20.0 (IBM Corporation, New York, USA) and EpiInfo™ version 6 (Center for Disease Control and Prevention, Atlanta, USA). For categorical data, frequencies (n) and percentages (%) were calculated and Chi-square (or Fisher’s exact when the count in a cell was ≤5) was used for determining intergroup differences. Relative risk with 95% confidence interval (CI) was expressed. For continuous data, mean ± standard deviation or median with interquartile range (IQR) were calculated based on normality distribution. Intergroup comparisons were performed using independent sample t-test or Kruskal–Wallis test. Binary logistic (dichotomous outcome) and multiple linear (continuous outcome) regression models were used to control for covariates that could influence pregnancy and birth outcomes. The adjusted risk or adjusted mean difference were generated. A P < 0.05 was considered statistically significant.

Results
During the study, 563 pregnant women were screened, of which 177 were included in the exposed and 354 in the unexposed group. Figure 1 gives the enrollment flowchart for the study population.

Maternal characteristics
The baseline characteristics of the cohort at enrollment are presented in Table 1. Primigravida, second, and multigravida constituted 35.0%, 35.6%, and 29.4% of the study population, respectively. Majority belonged to lower socioeconomic strata. Women in the exposed group were older than the unexposed. Approximately 45% of the women in the exposed and 37% of the women in the unexposed were underweight (body mass index <19.8 kg/m²). Although mean hemoglobin was ≥11.0 g/dL in both groups, it was significantly lower in the exposed group.

Bidi rolling practices in the exposed group
Women started bidi rolling at a median age of 20 (IQR 5) years and were exposed to tobacco for duration of eight (IQR 6) years at enrollment. They rolled approximately 600 (IQR 300) bidis a day and were exposed to 500–1000 g dry tobacco dust. None wore gloves or mask. Nearly three-fourths of the women stopped rolling at a median of 30 (IQR 8) gestational weeks due to the intense labor involved and transitioned to sorting and packaging bidis. In 69.5% of households, other family members were also bidi rollers.

Pregnancy and birth outcomes
Table 2 gives the pregnancy outcome in the two groups. The adjusted risks for hypertension during pregnancy and FGR were significantly higher in the exposed group. The adjusted risk for prematurity was not different between the groups. Table 3 gives the birth outcome of live-births in the two groups. GA at birth was comparable. Mean birth weight, length, and head circumference were lower in the exposed group. SGA was present in 31.2% in the exposed and 20.6% in the unexposed group. The risk for SGA in the exposed group was 1.51 (95% CI: 1.12, 2.04; P = 0.007). When controlled for age, parity, body mass index, anemia, hypertension, and gestational diabetes mellitus, the adjusted risk for SGA in the exposed group was significantly higher at 1.75 (95% CI: 1.12, 2.73; P = 0.015).

Evidence of nicotine absorption
A serum cotinine value ≥2 ng/mL was found in 38.3% of

| Table 1: Demography of the tobacco exposed and unexposed groups |
|---------------------------------------------------------------|
| **Variable** | **Exposed (n=177)** | **Unexposed (n=354)** | **Mean difference (95% CI)** | **Trend (P)** |
| Age (years) | 28.34±3.57 | 26.98±3.64 | 1.36 (0.71-2.01) | <0.001 |
| BMI (kg/m²) | 20.87±3.65 | 21.26±3.67 | −0.39 (−1.05-0.27) | 0.246 |
| Pregnancy weight gain (kg)* | 7.63±4.33 | 7.50±3.87 | 0.12 (−0.61-0.87) | 0.740 |
| Haemoglobin (g/dL) | 11.00±1.10 | 11.25±1.26 | −0.25 (−0.03–−0.46) | 0.024 |

*Excludes three early pregnancy losses (n=174). SD: Standard deviation, BMI: Body mass index, CI: Confidence interval
maternal and 29.6% of cord blood in the exposed group. The highest values were 125 ng/mL in the maternal and 110 ng/mL in the cord blood. Cotinine was detectable in 34.2% of pregnancies with adverse outcome. The median birth weights of infants born to mothers with and without evidence of nicotine absorption were not different (2830 g vs. 2860 g) as shown in Figure 2.

**DISCUSSION**

Adverse pregnancy outcomes were increased in women with occupational tobacco exposure through bidi rolling. Statistically significant findings included hypertension during pregnancy and FGR. Other than hypertension, these results are comparable to outcomes reported with maternal smoking.[5,8,9] An increased risk for preeclampsia has been reported with maternal use of snuff, another nonsmoking form of tobacco exposure.[16] Our results are consistent with this. On the contrary, maternal smoking has an inverse relationship with preeclampsia with OR ranging between 0.45 and 0.71.[5] One of the proposed pathogenesis of preeclampsia is an alteration in proteins that promote placental vasculature or angiogenesis.[17] Anti-angiogenic proteins released by a hypoxic placenta are considered to be the mediators for preeclampsia.[16,17] Carbon

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**Table 2: Pregnancy outcome of tobacco exposed and unexposed groups**

| Outcome                  | Exposed (n=177), n (%) | Unexposed (n=354), n (%) | Relative risk (95% CI) | Trend (P) | Adjusted risk (95% CI) | Trend (P) |
|--------------------------|------------------------|--------------------------|------------------------|-----------|------------------------|-----------|
| Anaemia                  | 70 (40.2)              | 134 (37.8)               | 1.06 (0.85-1.33)       | 0.598     | -                      | -         |
| Hypertension$a,b$        | 11 (6.2)               | 6 (1.7)                  | 3.74 (1.41-9.95)       | $\chi^2=8.05$; $P=0.004$ | 3.54 (1.21-10.31) | 0.021     |
| Gestational hypertension | 9 (5.1)                | 5 (1.4)                  | -                      | -         | -                      | -         |
| Preeclampsia             | 2 (1.1)                | 1 (0.3)                  | -                      | -         | -                      | -         |
| Gestational diabetes mellitus$a$ | 5 (2.9) | 5 (1.4) | 2.03 (0.59-6.91) | 0.310* | -                      | -         |
| Fetal growth restriction$^a,d$ | 24 (13.9) | 19 (5.4) | 2.58 (1.46-4.59) | $\chi^2=11.22$; $P<0.001$ | 2.71 (1.39-5.29) | 0.004     |
| Pregnancy losses         | 4 (2.2)                | 0                        | -                      | -         | -                      | -         |
| Placental abruption$^a$  | 1 (0.6)                | 0                        | -                      | -         | -                      | -         |
| Placenta previa$^a$      | 2 (1.1)                | 0                        | -                      | -         | -                      | -         |
| Preterm premature rupture of membrane$^a$ | 4 (2.3) | 4 (1.1) | 2.05 (0.52-8.08) | 0.297* | -                      | -         |
| Preeclampsia $^a$        | 12 (6.9)               | 11 (3.1)                 | 2.23 (1.00-4.96)       | $\chi^2=4.08$; $P=0.043$ | 1.81 (0.74-4.45) | 0.194     |
| Very preterm             | 4 (2.3)                | 0                        | -                      | -         | -                      | -         |
| Late preterm             | 8 (4.6)                | 11 (3.1)                 | -                      | -         | -                      | -         |

$a$Excludes three early pregnancy losses (n=174). $b$Adjusted for age, parity, body mass index, gestational diabetes mellitus, tobacco exposure. $c$Excludes all pregnancy losses (n=173). $d$Adjusted for age, parity, BMI, anemia, hypertension, gestational diabetes mellitus, tobacco exposure. *Fisher’s exact.

CI: Confidence interval, BMI: Body mass index

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**Table 3: Birth outcome in neonates born to tobacco exposed and unexposed groups**

| Outcome                      | Mean±SD | Mean difference (95%CI) | Trend (P) | Adjusted* mean difference (95%CI) | Trend (P) |
|------------------------------|---------|------------------------|-----------|-----------------------------------|-----------|
| Gestation (weeks)            | 38.17±2.02 | 38.47±1.12              | −0.30 (−0.62-0.03) | 0.071 | −0.16 (−0.43-0.11) | 0.242 |
| Birth weight (g)             | 2823.70±511.78 | 2993.23±462.68        | −169.53 (−256.88−82.19) | $t(525)=−3.81<0.001$ | −103.84 (−176.63-−31.04) | 0.005 |
| Length (cm)                  | 48.35±2.62 | 49.05±1.90              | −0.70 (−1.10−0.31) | $t(525)=−3.50<0.001$ | −0.45 (−0.77−0.13) | 0.006 |
| Head circumference (cm)      | 33.37±1.84 | 33.87±1.22              | −0.50 (−0.80−0.19) | $t(248)=−3.23<0.001$ | −0.36 (−0.58−0.14) | 0.002 |

*a*Adjusted for age, parity, BMI, weight gain, anemia, hypertension, gestational diabetes mellitus, gestation week, bidi rolling. CI: Confidence interval, BMI: Body mass index
monoxide in the combustion product decreases circulating anti-angiogenic proteins and inhibits placental tissue cellular death.\textsuperscript{[17]} Nicotine, on the other hand, decreases placental growth factor, an angiogenic protein, and increases placental tissue cellular death.\textsuperscript{[18]}

The risks for FGR and prematurity with maternal tobacco exposure due to abnormal placentation and alterations in placental function are well established.\textsuperscript{[3,4,6,9]} The adjusted risk for FGR seen in this study is comparable to that noted by Dejmek et al.\textsuperscript{[9]} in moderate smokers. The adjusted risk for prematurity was not significant in the present study. An increased risk of preterm births, especially very (<32 weeks) and extreme (<28 weeks) preterm births, has been reported with maternal smoking,\textsuperscript{[19]} snuff use,\textsuperscript{[20]} and tobacco chewing\textsuperscript{[22]} during pregnancy. Differences in the magnitude of tobacco exposure may be responsible for the discrepant results. Unlike active tobacco exposure in the aforementioned studies, tobacco exposure is passive in the present study. Of note, very preterm births were present only in the exposed group. However, statistical inference is not possible because of the small numbers.

Significantly lower newborn anthropometric measurements and a higher proportion of SGA were noted in the exposed group. The adjusted mean difference in birthweight seen in the present study is comparable to the decrement seen with moderate maternal active smoking reported in the United Kingdom Millennium study.\textsuperscript{[9]} The decrement is higher than that reported with maternal light smoking,\textsuperscript{[8]} environmental exposure to tobacco smoke,\textsuperscript{[9]} and smokeless tobacco exposures.\textsuperscript{[12,21]} There are no reports on the effect of maternal tobacco exposure on birth length, but a meta-analysis shows a 0.5 cm decrease in birth head circumference with maternal smoking.\textsuperscript{[22]} The adjusted risk for SGA in the exposed group is comparable to the risk reported in maternal snuff use.\textsuperscript{[21]}

Nicotine absorption was evident in approximately one-third of maternal and cord blood samples in the exposed group. During pregnancy, metabolism of both nicotine and cotinine increases by 60\% and 140\%, respectively, due to the induction of liver enzyme CYP2A6.\textsuperscript{[23]} There is also increased glucuronidation and oxidation, the other pathways of nicotine metabolism,\textsuperscript{[23,24]} which may explain our results. The existence of variant alleles such as CYP2A6*4 with lower cotinine levels has been reported among the Asians.\textsuperscript{[25]}

Women in the exposed group were interviewed at every visit for bidi rolling practices; the women in the unexposed group were screened for nondisclosure using serum cotinine determination. Standard definitions were used for all outcomes, and accuracy of clinical and sonographic data was ensured. These are some of the strengths of the study. A limitation of the study is that a tobacco exposure index could not be stratified as is possible with active smoking or tobacco chewing.\textsuperscript{[5,9,12,16]} Cotinine was the only biomarker studied. Bidi rolling practices and cotinine values could not be correlated. Demonstration of nicotine or cotinine in hair for chronic exposure\textsuperscript{[21]} was out of the scope of this study.

\section*{Conclusion}

The study results support the hypothesis that occupational tobacco exposure due to bidi rolling and handling leads to adverse pregnancy and birth outcomes. The magnitude of the findings was comparable to moderate maternal active smoking.

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\section*{Conflicts of interest}

There are no conflicts of interest.

\section*{References}

1. International Labour Organisation. Making Ends Meet: Bidi Workers in India Today. Study of Four States. Geneva: International Labour Organisation; 2003. Available from: http://www.iolo.org/public/english/dialogue/sector/papers/food/wp202.pdf. [Last accessed on 2018 Jan 20].

2. Zorin S, Kuylenstierna F, Thulin H. In vitro test of nicotine’s permeability through human skin. Risk evaluation and safety aspects. Ann Occup Hyg 1999;43:405-13.

3. Lambers DS, Clark KE. The maternal and fetal physiologic effects of nicotine. Semin Perinatol 1996;20:115-26.

4. U.S. Department of (HHS) Health and Human Services 2014. Reproductive outcomes. The Health Consequences of Smoking: 50 Years of Progress. Report of the Surgeon General. Ch. 9. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. p. 459-521. Available from: https://www.surgeongeneral.gov/library/reports/50-years-of-progress/sgr50-chap-9.pdf. [Last accessed on 2018 Feb 12].

5. U.S. Department of (HHS) Health and Human Services 2004. Reproductive effects. The Health Consequences of Smoking: A Report of the Surgeon General. Ch. 5. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004. p. 525-610. Available from: https://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/chapter 5.pdf. [Last accessed on 2018 Feb 10].

6. Xiao D, Huang X, Yang S, Zhang L. Direct effects of nicotine on contractility of the uterine artery in pregnancy. J Pharmacol Exp Ther 2007;322:180-5.

7. Janssen BG, Gyselaers W, Byun HM, Roels HA, Cuypers A, Baccarelli AA, \textit{et al}. Placental mitochondrial DNA and CYP1A1 gene methylation as molecular signatures for tobacco smoke exposure in pregnant women and the relevance for birth weight. J Transl Med 2017;15:5.

8. Ward C, Lewis S, Coleman T. Prevalence of maternal smoking and environmental tobacco smoke exposure during pregnancy and impact on birth weight: Retrospective study using millennium cohort. BMC Public Health 2007;7:81.

9. Dejmek J, Solansky J, Podrazilová K, Srám RJ. The exposure of nonsmoking and smoking mothers to environmental tobacco smoke during different gestational phases and fetal growth. Environ Health Perspect 2002;110:601-6.
10. Leonardi-Bee J, Smyth A, Britton J, Coleman T. Environmental tobacco smoke and fetal health: Systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2008;93:F351-61.

11. Juárez SP, Merlo J. The effect of Swedish snuff (snus) on offspring birthweight: A sibling analysis. PLoS One 2013;8:e65611.

12. Gupta PC, Subramoney S. Smokeless tobacco use, birth weight, and gestational age: Population based, prospective cohort study of 1217 women in Mumbai, India. BMJ 2004;328:1538.

13. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. Lancet Glob Health 2013;1:e26-36.

14. Sardesai SP, Shinde NS, Patil SB, Rayate MN, Muley B. Tobacco handling by pregnant Bidi workers: As hazardous as smoking during pregnancy. J Obstet Gynecol India 2007;57:335-8.

15. Mandelia C, Subba SH, Yamini. Effects of occupational tobacco exposure on foetal growth, among beedi rollers in coastal Karnataka. J Clin Diagn Res 2014;8:JC01-4.

16. Wikström AK, Stephansson O, Cnattingius S. Tobacco use during pregnancy and preeclampsia: Effects of cigarette smoking and snuff. Hypertension 2010;55:1254-9.

17. Karumanchi SA, Levine RJ. How does smoking reduce the risk of preeclampsia? Hypertension 2010;55:1100-1.

18. Wong MK, Barra NG, Alfayad N, Hardy DB, Holloway AC. Adverse effects of perinatal nicotine exposure on reproductive outcomes. Reproduction 2015;150:R185-93.

19. Qiu J, He X, Cui H, Zhang C, Zhang H, Dang Y, et al. Passive smoking and preterm birth in urban China. Am J Epidemiol 2014;180:94-102.

20. Baba S, Wikström AK, Stephansson O, Cnattingius S. Influence of smoking and snuff cessation on risk of preterm birth. Eur J Epidemiol 2012;27:297-304.

21. Baba S, Wikström AK, Stephansson O, Cnattingius S. Changes in snuff and smoking habits in Swedish pregnant women and risk for small for gestational age births. BJOG 2013;120:456-62.

22. Ekblad M, Korkela J, Lehtonen L. Smoking during pregnancy affects foetal brain development. Acta Paediatr 2015;104:12-8.

23. Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol 2009;192:29-60.

24. Bowker K, Lewis S, Coleman T, Cooper S. Changes in the rate of nicotine metabolism across pregnancy: A longitudinal study. Addiction 2015;110:1827-32.

25. Xie C, Wen X, Ding P, Liu T, He Y, Niu Z, et al. Influence of CYP2A6 *4 genotypes on maternal serum cotinine among Chinese nonsmoking pregnant women. Nicotine Tob Res 2014;16:406-12.