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The effect of tobacco use and other determinants on pregnancy outcomes: a multi-center hospital based case control study in Karachi, Pakistan

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Abstract

Objectives: The objective of this study was to identify the effects of maternal tobacco consumption during pregnancy on birth outcomes and obstetric complications in Karachi, Pakistan.

Setting: A multi-center hospital based case control study was conducted in Karachi, the largest city of Pakistan.

Participants: A random sample of 1275 women coming to the gynecology & obstetric department of selected hospitals for delivery was interviewed within 48 hours of delivery from wards. Cases were women with adverse birth outcomes and obstetric complications while controls were women with who had normal delivery without any complications.

Primary and secondary outcome measures: Adverse birth outcomes (preterm delivery, low birth weight, still birth, low APGAR score) and obstetric complications (antepartum hemorrhage, cesarean section etc.)

Results: The final multiple logistic regression analysis revealed that with every one year increase in age the odds of being a case was 1.03 times as compared to being a control. Exposure to tobacco (adjusted OR (aOR) : 2.24; 95% Confidence Interval (CI): 1.56-3.23) , having no slits in the kitchen (proxy indicator for indoor air pollution) (aOR= 1.90; 95% CI: 1.05 – 3.43), gravidity (aOR= 0.83; 95% CI: 0.73-0.93), non-booked hospital cases (aOR= 1.87; 95% CI: 1.38-2.74), history of still birth (aOR= 4.06; 95% CI: 2.36 – 6.97) , miscarriages (aOR= 1.91; 95% CI: 1.27 – 2.85) and preterm delivery (aOR= 6.04; 95% CI: 2.52- 14.48) were significantly associated with being a case as compared to control.

Conclusions:

This study suggests that women who had adverse pregnancy outcomes were more likely to have exposure to tobacco, previous history of adverse birth outcomes and were non booked cases.

Health professionals should be educated about risk factors for adverse pregnancy outcomes and obstetric complications Pre-natal care and health education during the antenatal period might help in preventing such adverse events.

Keywords: Preterm birth, Smoking, Maternal tobacco use, Low birth weight, Stillbirth, Tobacco smoke

Strengths and Limitations of this study

• Our study included a robust method of recruitment to reduce classification of the outcome.

• Being a multicenter study catering to patients from different ethnic and socioeconomic backgrounds enhanced generalizability of our results.

• One of the limitations of this study was that most of the information was self-reported, therefore, it was prone to reporting bias.

• Ideally, serum cotinine levels would have been a better measure; however, it was not possible to obtain blood samples in our study.

INTRODUCTION

Globally, tobacco use is a major public health problem. According to the World Health Organization (WHO), there are about one billion smokers worldwide with an increase in the use of tobacco products, especially in developing countries [1]. Tobacco use is common in Pakistan; about 34% of men and 12.5% of women use different forms of tobacco regularly [2]. Also striking is the fact that 3.2 % of pregnant women had ever been a regular cigarette smoker in Pakistan [3]. Smoking prevalence among women varies markedly across countries; it is 7% in developing countries and 24% in developed countries [2]. Epidemiological evidence from many countries indicate tobacco smoking as an important risk factor in lung diseases, ischemic heart disease, and obstructive peripheral vascular disease [4]. Additionally, women cigarette smokers have higher rate of gynaecological complications [5] and decreased fertility potential [6-8]. Smoking increases the level of nicotine and carbon monoxide in the blood which causes serious complications including increased rate of spontaneous abortion [9], premature delivery [9 10] low birth weight [9 11 12] placenta praevia, bleeding during pregnancy, premature rupture of membranes and stillbirths [13-15]. Other adverse outcomes include Small for Gestational Age (SGA) babies [11 16] miscarriages [17], lipid abnormalities [18], increased risk for hypertension, gestational diabetes [19] and reduced reproductive capability [20]. Tobacco use increases perinatal mortality to one and a half times the average rate [21-23].

Another important aspect is the increasing use of alternative forms of tobacco. According to the National Health Survey (NHS) of Pakistan, nearly 10% of females aged 25-64 years reported regular use of chewing tobacco or snuff and over 7% of women smoked chillum or huqqa. Additionally, smokeless tobacco use is increasingly associated with maternal cigarette smoking [21 24-28]. Tobacco use, either chewed, applied orally, or smoked actively or passively, increases

stillbirths by nearly three folds, reduces birth weight by 100-400 gm, significantly increases placental weight and is also associated with high fetal mortality [25]. The impact of smoking on women's health deserves special attention, as women are susceptible to almost all of the tobacco health hazards that men are exposed to. The NHS reported that 31% of pregnant women who had ever tried cigarette smoking had transitioned to regular use. Among the few pregnant women who had ever smoked regularly, 76.9% admitted to currently smoking [2]. Notably, the majority (92%) of these women reported that smoking cigarettes or other tobacco products was permitted in their home. About half (49.9%) of the women reported having been frequently or always exposed to indoor tobacco smoke, whereas, 51.4% reported that their young children were frequently or always exposed to indoor tobacco smoke. This has important implications as women and children are the most vulnerable in terms of experiencing the adverse effects of tobacco use. Passive smoking has been found to be associated with preterm birth [29 30] and LBW [31] among pregnant women.

Most of the studies conducted in Pakistan on tobacco use have either been cross sectional surveys [2] or have focused primarily on school children [32] and adolescents [33 34]. Very few studies have focused on pregnant women and tobacco consumption [2]. To our knowledge, this is the first case control study from Pakistan to identify the effects of maternal tobacco consumption during pregnancy on birth outcomes and obstetric complications.

MATERIAL AND METHODS

The study was designed as a multicenter hospital based case control study in Karachi, Pakistan. Karachi is the largest metropolitan city of Pakistan with a population estimated to be about 20 million [35]. Study participants were enrolled from four leading maternity hospitals of Karachi (Civil Hospital, Jinnah Postgraduate Medical College Hospital, Lyari General Hospital and

Sobhraj Maternity Hospital) from March to December, 2011. The study population comprised of all pregnant women aged 16 to 45 years, coming to the selected hospitals from different ethnic, social, cultural and economic groups.

Inclusion Criteria

Cases

Infants:

Cases were infants with the following outcomes: Low birth weight (< 2.5 kg) babies, still births (Any child delivered after the 28th week of pregnancy who does not breathe afterwards or show any signs of life) and intra uterine deaths (fetus dies in uterus before labor starts).

Mothers:

Any women presenting with the following outcomes were enrolled as cases:

a) Cesarean section due to Fetal distress: (decreased heart rate <100 beats/min and /or passing meconium during labour) b) Antepartum hemorrhage: (bleeding from the vagina occurring at any time after 28th week of pregnancy and before the birth of the child) c) Abruptio placentae: Hemorrhage due to the partial separation of a placenta normally situated on the upper segment of the uterus d) Placenta praevia: Hemorrhage due to the partial separation of a placenta abnormally situated on the lower segment of the uterus e) Preterm labor (labor occurring before the 37th week of pregnancy) f) Abnormal uterine action-Prolonged labour: Failed indication (Delay in labor) due to primary uterine hypotonia in which contractions are weak, short and infrequent.

Controls

Women with term deliveries (37-40 weeks) having the following outcomes:

a) Normal Vaginal deliveries with or without episiotomy b) Normal vaginal assisted (forceps or vacuum) deliveries c) Cesarean sections due to cephalo-pelvic disproportion (obstructed labor), malpresentation of fetus and cord around the neck.

Exclusion Criteria

Women with history of diabetes mellitus, gestational diabetes, hypertension before pregnancy, pre-eclampsia, eclampsia, severe anemia (Hemoglobin <8 mg), cardiovascular diseases (valvular defects, congestive failures etc), chronic obstructive pulmonary disease, renal diseases, active infections (tuberculosis, hepatitis), epilepsy and severe complications in previous pregnancies were excluded from the study.

Sampling strategy

Each hospital was treated as a stratum and pregnant women were selected randomly from hospitals by using hospital lists. To determine sample size, a value of α =0.05 and β=0.2 was specified and an OR of 1.6 was assumed. In Pakistan, approximately 25% of newborns have LBW [36]. The required sample size was 1275 individuals with a design effect of 1.1[36] and 10% non-response rate. A case to control ratio of 1:3 was used. The estimated sample size for examining factors associated with LBW was larger than the sample size to examine other adverse pregnancy outcomes, so the larger sample size was selected.

A proportionate stratification technique was used to draw the samples from each hospital. In this technique, sample size of each stratum is proportionate to the population size of the stratum. The average number of delivered ladies was calculated in all five hospitals. Proportions (weight) of delivered ladies in each hospital were calculated by taking ratio between number of delivered ladies in each hospital and total number of delivered ladies in all five hospitals. The total number of deliveries was multiplied by calculated proportions (weight) of each hospital.

Enrollment of cases and controls

Trained data collectors interviewed mothers in obstetrics and gynecology wards of the selected hospitals within 48 hours of delivery. Based on the case and control definition, the registers of the wards were searched for study participants who were selected randomly and then approached for interviews after receiving their consent.

Definition of tobacco users

All women who had used tobacco products (smoke and smokeless) for the past six-months [22] were considered as tobacco users.

Data Collection procedure/ Tool

One research coordinator and three female data collectors were hired for data collection which were trained by the Principal Investigator. Written approval was taken from all the hospitals' administration to recruit their patients in the study. Data collectors checked hospital records daily to obtain information about the expected number of women delivering babies on the day of visit to the hospitals. Field team visited the normal vaginal delivery room, recovery room and intensive care unit on a daily basis to gather the required information. After selection, an informed consent was taken from each woman. Study participants were explained the purpose of the study and any queries were addressed. After the interview, data collectors provided information to subjects about ill effects of tobacco use during pregnancy

Questionnaire

The questionnaire was developed in English and then translated into Urdu. The questionnaire contained questions regarding maternal socio-demographic information, nutrition, previous and current obstetric characteristics, physical condition and tobacco consumption in any form during

pregnancy. The last part of questionnaire focused on the main outcome of the study; Apgar score (< 7), weight of newborn, caesarean section, preterm birth and stillbirth.

Ethical consideration

Ethical approval for the study was obtained from the Aga Khan University's Ethical Review Committee (ERC). Written consent was obtained from all the hospitals' administration and individuals before an interview. Every precaution was taken to respect the privacy of subject.

Data editing and entry

The principal investigator and the data collectors edited filled questionnaires on a daily basis in the field and office. Data were double entered by two data entry operators in Epi-info version 6.04 [37].

Statistical analysis

Analyses were performed using STATA version 12.0. Descriptive analysis was carried out by calculating mean and standard deviation for continuous variables, and proportions for categorical variables. Logistic regression analysis was performed to study the associations between tobacco use and other factors and adverse pregnancy outcomes [38]. Crude odds ratio (OR) and their 95% confidence interval (CIs) were calculated. Those variables with p-value ≤0.25 or biological or social importance were selected for multiple logistic regression analysis [38]. Adjusted odds ratios (AOR) and their 95% CIs were obtained from multiple logistic regression model. All biologically plausible interactions were evaluated.

RESULTS

A total of 1275 (312 in cases and 963 in control group) women with singleton births were recruited for this study. The median duration of marriage were 3 years (IQR = 1.0-7.0 years) among cases and 5 years (IQR= 3.0-9.0 years) among controls with median gravidity of 2 children in both groups. The number of mothers who had suffered from at least one of these complications like urinary tract infection, hypertension, gestational diabetes, vaginal discharge/bleeding, excessive vomiting, pre-mature rupture of membrane or regular breathlessness during the recent pregnancy was high, that is 120 (38.5%) in cases and 198 (20.6%) in control group. About 42.3% cases and 24.4% controls were exposed to tobacco. Exposure to tobacco between case (with adverse birth outcome) and controls was found to be significantly different (Table 1).

Cases included 312 participants consisting of 62 preterm, 15 still births, 9 intrauterine deaths, and 137 with weight less than 2.5 kg. The average weight of baby among cases was 2.5 Kg (SD = 0.6 Kg) and there were a total of 216 babies delivered by caesarian section. The control group comprised of 963 women without any of these conditions (Table 2).

Binary logistic regression analysis showed a significant association between exposed to tobacco [chew, smoke (active/passive)] with adverse pregnancy outcome at the univariable level (OR: 2.27; 95% CI: 1.73-2.97). The estimated odds ratios of women who has history of any illness (hypertension/ ischemic heart disease/ diabetes/ tuberculosis/ asthma/ liver disease), history of miscarriage, preterm delivery, still birth, complication during previous pregnancy, complication during current pregnancy are significantly higher among the women with adverse birth outcomes (cases) compared to those without adverse birth outcomes (controls) (Table 3).

Age of women was also associated with adverse pregnancy outcome. For educational level, family history of illness, and gestational age, there were no significant difference found between cases and controls. Cases were more likely to cook in kitchens without a slit/window (a proxy indicator for indoor pollution) (OR=1.7; 95% CI: 1.1 -2.8) as compared to controls.

The final multiple logistic regression analysis indicated that the odds of exposure to tobacco smoke (active/passive) among cases were 2.24 times compared to controls (OR: 2.24; 95% CI: 1.56-3.23) after adjusting for other variables in the model. Age (adjusted OR= 1.03; 95% CI: 1.0-1.1), no slits in the kitchen (adjusted OR: 1.90; 95% CI: 1.05-3.43), gravidity (adjusted OR= 0.83; 95% CI: 0.73-0.93), non-booked hospital cases (adjusted OR= 1.87; 95% CI: 1.38-2.74), history of still birth (adjusted OR= 4.06; 95% CI: 2.36-6.97), miscarriages (adjusted OR= 1.91; 95% CI: 1.27-2.85) and history of preterm delivery(adjusted OR= 6.04; 95% CI: 2.52- 14.48) were significantly associated with being a case as compared to control (Table 4).

DISCUSSION

In our study smoking (active or passive) was significantly associated with adverse pregnancy and obstetrics complications. Previous epidemiological studies have also reported that active smoking [39-44] and passive smoking [12 45 46] is associated with preterm delivery. Smoking during pregnancy releases carbon monoxide and/or nicotine which induce fetal hypoxia. Fetal haemoglobin has a higher affinity for carbon monoxide than adult haemoglobin and the impact on the fetus is more severe than on the mother. Our study identified smoking as a very important risk factor for adverse pregnancy outcomes in Pakistani population; therefore, counselling of pregnant females about the detrimental effects of smoking (active/passive) is warranted.

Our study indicates that having no slits or windows in the kitchen; a proxy indicator for indoor air pollution resulted in an increased risk of adverse birth outcomes. Indoor air pollution (IAP) is

one of the major risk factors for pneumonia related morbidity, low birth weight and death in children worldwide [47]. In Pakistan, the use of wood for cooking fuel is common (>53%) and overall biomass use including wood, crop residues, and animal dung is >70% [47]. It is plausible that smoke or particulate matter during cooking could have an adverse effect on pregnant women [48]. There is a dearth of scientific studies in Pakistan which relate IAP to health effects [47]. Studies from developed countries suggest that particulate of IAP and ambient air pollution has an association with LBW [49 50]. Furthermore, reports from developing countries have described an association between the use of biomass fuels in open fires for cooking and LBW [51 52] preterm birth [53] and SGA [54]. Analyses from the Second National Family Health Survey of India (1998–99) reported the occurrence of stillbirths related to the use of biomass cooking fuel [55] whereas the Third National Family Health Survey (2005-06) reported an association between biomass cooking fuel and lower birth weight [56], findings which are consistent with our study. In our study, we found that increasing age of the female was significantly associated with adverse pregnancy outcomes, a finding supported by several studies [57-59]. Pregnant women aged 35 years or older experience an increased risk of intrauterine fetal death, pregnancy-induced hypertension, and gestational diabetes [60]. Our study also identified women having previous history of stillbirth, miscarriage and preterm deliveries to be associated with adverse birth outcomes which is consistent with another study that compared females with no history of abortion, with females who had one, two and three or more previous abortions [37].The prevalence of LBW babies among these females was 2.8, 4.6 and 9.5 times respectively. The risk for preterm birth was also 1.7, 2.0 and 3.0 times higher for women with a history of one, two and three or more previous abortions, respectively [61].

Our study results also indicate that the cases were less likely to be booked at the hospital as compared to controls. The cases in our study had a history of previous miscarriages and still births predisposing them to higher risk of adverse pregnancy outcomes. Therefore, it was imperative for them to be booked at the hospital apriori so that better treatment options could be given to them to prevent such complications.

Another important finding was that blood transfusion was significantly associated with adverse pregnancy outcomes. Anemia, a proxy indicator for blood transfusion is usually detected when doctors do a routine complete blood count at the first examination after pregnancy is confirmed. If anemia persists the fetus may not receive enough oxygen, and the risk of preterm is increased. Bleeding that occurs normally during labor and delivery can also dangerously worsen anemia in these women. In our study cases may be unaware of their hemoglobin status and may have been severely anemic because of missed pre-natal checkups, therefore, at the time of delivery may be in desperate need of blood transfusion. Thus the severity of anemia among these females might have led to the adverse pregnancy outcomes. However, in our study we were unable to retrieve information regarding the hemoglobin levels of the pregnant female.

Gravidity showed an inverse association with adverse birth outcomes. This association needs to be explored further to determine if women who experienced previous pregnancies are more likely to take better care of themselves during future pregnancies. Strengths of our study included a robust method of recruitment to reduce misclassification of the outcome and being a multicenter study catering to patients from different ethnic and socioeconomic backgrounds, thereby enhancing generalizability of our results. One of the limitations of this study was that most of the information was self-reported, therefore, it was prone to reporting bias [62]. Ideally,

serum cotinine levels would have been a better measure; however, it was not possible to obtain blood samples in our study.

CONCLUSION

Our study identified smoking as a very important risk factor for adverse birth outcomes. Moreover, indoor air pollution, previous history of stillbirth, miscarriage, preterm deliveries, increasing maternal age, non-booked cases and improper ventilation were also important predictors for adverse pregnancy outcomes. Our study underscores the importance of ante-natal care during pregnancy. We recommend education of health professionals about risk factors for adverse pregnancy outcomes and obstetric complications. Interventions aimed at improving pre-natal care and health education during the antenatal period might help in preventing such adverse events.

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Author's note

SR contributed to analysis, interpretation, manuscript drafting and reviewing. ZAB and NZ were responsible for manuscript writing, and reviewing the paper. SW helped in data cleaning, management, and analysis. KS contributed to manuscript drafting and reviewing the paper.

Declaration of Conflicting interests

The authors declare that there is no conflict of interest.

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Data Sharing

No additional unpublished data are available.

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Table 1. Characteristics of cases and controls presenting at selected hospitals in Karachi, Pakistan

Characteristics		Cases n (%)	Controls n (%)
Age of mother (Years)			
Mean (S.D)		25.3 (4.8)	26.0 (4.6)
Mother tongue of respondent			
Urdu		168 (53.8)	492 (51.1)
Sindhi		31(9.9)	88 (9.1)
Punjabi		20 (6.4)	79 (8.2)
Balochi		28 (9.0)	99 (10.3)
Pashto		31 (9.9)	111 (11.5)
Others		34 (10.9)	94 (9.8)
Educational level			
No formal education		114 (36.5)	353 (36.7)
Primary & secondary		160 (51.3)	519 (53.9)
Intermediate		26 (8.3)	66 (6.9)
Graduate & post graduate		12 (3.8)	25 (2.6)
Religion			
Muslim		302 (96.8)	937 (97.3)
Christian		1 (0.3)	8 (0.8)
Hindu		9 (2.9)	18 (1.9)
Family system			
Nuclear		106 (34.0)	356 (37.0)
Joint		206 (66.0)	607 (63.0)
Nature of house			
Kachchaa		14 (4.5)	21 (2.2)
Pakka		298 (95.5)	942 (97.8)
Work currently			
No		307 (98.4)	952 (98.9)
Yes		5 (1.6)	11 (1.1)
Gravidity	Med (IQR)	2.0 (1.0 – 3.0)	2.0 (3.0 - 4.0)
Years of marriage	Med (IQR)	3.0 (1.0 - 7.0)	5.0 (3.0 – 9.0)
No. of antenatal care visits			
Mean (S.D		6.6 (3.6)	6.5 (3.2)
Ever domestic violence			
No		306 (98.1)	947 (98.3)
Yes		6 (1.9)	16 (1.7)
Gestational age when fetal movement started (Weeks)			
Mean (S.D)		20.7 (2.3)	20.7 (2.2)

Table 1. Continued.

Complication during current pregnancy		
No	192 (61.5)	765 (79.4)
Yes	120 (38.5)	198 (20.6)
Immunization done during this pregnancy		
No	65 (20.8)	216 (22.4)
Yes	247 (79.2)	747 (77.6)
Ultrasound done during this pregnancy		
No	8 (2.6)	19 (2.0)
Yes	304 (97.4)	944 (98.0)
Duration between water break and delivery of baby (Hours) Med(IQR)	13.0 (6.0 – 36.0)	6.0 (2.0 – 14.0)
Material/fuel use for cooking		
Gas	291 (93.3)	905 (94.0)
Wwood & others	21(6.7)	58 (6.0)
Slits/window in the kitchen		
No	29 (9.3)	54 (5.6)
Yes	283 (90.7)	909 (94.4)
Slits/window in the house		
No	12 (3.8)	26 (2.7)
Yes	300 (96.2)	937 (97.3)
Exhaust fan in kitchen		
No	277 (88.8)	834 (86.6)
Yes	35 (11.2)	129 (13.4)
Average time spend in kitchen while stove burning (hours) Mean(S.D)	1.9 (0.9)	1.9 (0.9)
Exposed to tobacco		
No	180 (57.7)	728 (75.6)
Yes	132 (42.3)	235 (24.4)

Table 2: Distribution of adverse pregnancy outcomes and obstetric complications among cases and controls at selected hospitals in Karachi, Pakistan

Outcome	Cases n (%)	Controls n (%)
Preterm delivery		
No	250 (80.1)	963 (100)
Yes	62 (19.8)	-
Caesarian section		
No	96 (30.8)	596 (61.9)
Yes	216 (69.2)	367 (38.1)
Status of baby at birth		
Alive	288 (92.3)	963 (100.0)
IUD	9 (2.9)	-
Still birth	15 (4.8)	-
Birth weight of baby (kg)		
Mean(S.D)	2.5 (0.6)	3.0 (0.4)

Table 3: Univariate analysis of factors associated with adverse birth outcomes and obstetric complications among cases and controls at selected hospitals in Karachi, Pakistan

Characteristics	Controls n = 963	Cases n =312	Crude Odds ratio (OR)	95% CI
Age of Mother (Years)				
Mean (SD)	26.0 (4.6)	25.3 (4.8)	0.96	(0.90-1.0)
Educational Level				
No Formal education	353 (36.7)	114 (36.5)	1	-
Primary & Secondary	519 (53.9)	160 (51.3)	0.95	(0.73-1.25)
Intermediate	66 (6.9)	26 (8.3)	1.22	(0.74-2.01)
Graduate and Post graduate	25 (2.6)	12 (3.8)	1.49	(0.72-3.05)
Nature of house				
Kachchaa	21 (2.2)	14 (4.5)	1	-
Pakka	942 (97.8)	298 (95.5)	2.11	(1.10- 4.21)
Mother's history of illness				
No	959 (99.6)	305 (97.8)	1	-
Yes	4 (0.4)	7 (2.2)	5.50	(1.60- 18.92)
Family history of illness				
No	556 (57.7)	191(61.2)	1	-
Yes	407 (42.3)	121(38.8)	0.86	(0.72-1.10)
Years of marriage Mean(S.D)	6.1 (5.5)	4.6 (4.6)	0.90	(0.91- 1.00)
Gravidity Mean(S.D)	3.1 (0.1)	2.4 (0.1)	0.82	(0.80-0.91)
History of miscarriage				
No	565 (74.0)	110 (64.0)	1	-
Yes	198 (26.0)	62 (36.0)	1.61	(1.13-2.31)
History of preterm delivery				
No	752 (98.6)	158 (91.9)	1	-
Yes	11(1.4)	14 (8.1)	6.00	(2.71-13.60)
History of still birth				
No	718 (94.1)	142 (82.6)	1	-
Yes	45 (5.9)	30 (17.4)	3.34	(2.13-5.52)
Complication during previous pregnancy				
No	855 (88.8)	261 (83.7)	1	-
Yes	108 (11.2)	51 (16.3)	1.52	(1.10-2.21)

Table 3. Continued.

Booked in the hospital				
Yes	732 (76.0)	204 (65.4)	1	
No	231 (24.0)	108 (34.6)	1.70	(1.32-2.20)
Gestational age when fetal movement started (Weeks)				
Mean(S.E)	20.7 (0.1)	20.7 (0.1)	0.99	(0.94 -1.11)
No. of antenatal care visits	6.5 (0.1)	6.6 (0.2)	1.02	(0.99-1.04)
Micturition problem during pregnancy				
No	793 (82.3)	229 (73.4)	1	
Yes	170 (17.7)	83 (26.6)	1.71	(1.33-2.30)
Taken folic acid tablets				
No	611 (63.4)	199 (63.8)	1	
Yes	352 (36.6)	113 (36.2)	1.02	(0.81-1.30)
Complication during current pregnancy				
No	765 (79.4)	192 (61.5)	1	
Yes	198 (20.6)	120 (38.5)	2.40	(1.80-3.22)
Blood transfusion done				
No	914 (94.9)	286 (91.7)	1	
Yes	49 (5.1)	26 (8.3)	1.70	(1.0-2.80)
Duration between water break and delivery of baby (Hours)				
Mean(S.E)	12.3 (0.7)	27.8 (4.6)	1.03	(1.02-1.03)
Slits/window in the kitchen				
Yes	909 (94.4)	283 (90.7)	1	
No	54 (5.6)	29 (9.3)	1.72	(1.11-2.76)
Exposed to tobacco				
No	728 (75.6)	180 (57.7)	1	
Yes	235 (24.4)	132 (42.3)	2.27	(1.73 -2.97)

Table 4. Multivariate analysis of factors associated with adverse birth outcomes & obstetric complications among cases and controls at selected hospitals in Karachi, Pakistan

Characteristics	Adjusted odds ratio	95 % C.I
Exposure to tobacco smoke		
No	1	
Yes	2.24	(1.56-3.23)
Gravidity	0.83	(0.73-0.93)
Age of mother	1.03	(1.0-1.10)
Booked in hospital		
Yes	1	
No	1.87	(1.38-2.74)
History of Preterm births		
No	1	
Yes	6.04	(2.52- 14.48)
History of miscarriage		
No	1	
Yes	1.91	(1.27 – 2.85)
History of still birth		
No	1	
Yes	4.06	(2.36 – 6.97)
Slit/window in kitchen		
Yes	1	
No	1.90	(1.05 – 3.43)
Blood transfusion done		
No	1	
Yes	3.06	(1.68 – 5.57)

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Association of Tobacco Use And Other Determinants with Pregnancy Outcomes: A Multi-center Hospital Based Case Control Study in Karachi, Pakistan

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Abstract

Objectives: The study aimed to identify the effects of maternal tobacco consumption during pregnancy and other factors on birth outcomes and obstetric complications in Karachi, Pakistan.

Design: A multi-center hospital based case control study.

Setting: Four leading maternity hospitals of Karachi.

Participants: A random sample of 1275 women coming to the gynecology & obstetric department of selected hospitals for delivery was interviewed within 48 hours of delivery from wards. Cases were women with adverse birth outcomes and obstetric complications while controls were women with who had normal uncomplicated delivery.

Primary and secondary outcome measures: Adverse birth outcomes (preterm delivery, low birth weight, still birth, low APGAR score) and obstetric complications (antepartum hemorrhage, cesarean section etc.)

Results: Final multiple logistic regression analysis revealed that with every one year increase in age the odds of being a case was 1.03 times as compared to being a control. Exposure to tobacco (adjusted OR (aOR) : 2.24; 95% Confidence Interval (CI): 1.56-3.23) , having no slits in the kitchen (proxy indicator for indoor air pollution) (aOR= 1.90; 95% CI: 1.05 – 3.43), gravidity (aOR= 0.83; 95% CI: 0.73-0.93), non-booked hospital cases (aOR= 1.87; 95% CI: 1.38-2.74), history of still birth (aOR= 4.06; 95% CI: 2.36 – 6.97), miscarriages (aOR= 1.91; 95% CI: 1.27 – 2.85) and preterm delivery (aOR= 6.04; 95% CI: 2.52- 14.48) were significantly associated with being a case as compared to control.

Conclusions:

This study suggests that women who had adverse pregnancy outcomes were more likely to have

exposure to tobacco, previous history of adverse birth outcomes and were non booked cases. Engagement of stakeholders in tobacco control for; providing health education, incorporating tobacco use in women in the tobacco control policy and designing interventions for tobacco use cessation is warranted. Pre-natal care and health education might help in preventing such adverse events.

Keywords: Preterm birth, Smoking, Maternal tobacco use, Low birth weight, Stillbirth, Tobacco smoke

Strengths and Limitations of this study

• Our study included a robust method of recruitment to reduce classification of the outcome.

• Being a multicenter hospital based study catering to patients from different ethnic and socioeconomic backgrounds enhanced generalizability of our results.

• One of the limitations of this study was that most of the information was self-reported, therefore, it was prone to reporting bias. However, we had given extensive training to our data collectors to retrieve participant's information as accurately as possible.

• Ideally, serum cotinine levels would have been a better measure; however, it was not possible to obtain blood samples in our study

INTRODUCTION

Low birth weight (LBW) of the infant is a challenging multifaceted public health problem as. It varies from 4.5% in most developed countries to almost 50% in some of the least developed countries [1] .The prevalence of LBW is high in developing countries (18.5 %), with the highest prevalence in South Asia (27 %) including Pakistan [2] and India [1]. Still birth is another important adverse birth outcome. Globally, 3.9 million stillbirths are reported, and unfortunately 97% of them are occurring in the developing world [3].

There are a number of risk factors that may be associated with adverse birth outcomes and obstetric complications. Among them, tobacco use is a major public health problem globally. According to the World Health Organization, there are about one billion smokers worldwide [4]. Smoking prevalence among women varies markedly across countries; it is 7% in developing countries and 24% in developed countries [5]. Tobacco use is common in Pakistan; about 34% of men and 12.5% of women use different forms of tobacco regularly [5]. Notably, 3.2 % of pregnant women had ever been a regular cigarette smoker in Pakistan [6]. Women who smoke cigarettes have higher rate of gynaecological complications [7] and decreased fertility potential [8-10]. Smoking increases the level of nicotine and carbon monoxide in the blood which causes serious complications including increased rate of spontaneous abortion [11], premature delivery [11 12] low birth weight [11 13 14] placenta praevia, bleeding during pregnancy, premature rupture of membranes and stillbirths [15-17]. Other adverse outcomes include Small for Gestational Age (SGA) babies [13 18] miscarriages [19], lipid abnormalities [20], increased risk for hypertension, and gestational diabetes [21].

Another important aspect is the increasing use of alternative forms of tobacco. According to the National Health Survey (NHS) of Pakistan, nearly 10% of females aged 25-64 years reported

regular use of chewing tobacco or snuff and over 7% of women smoked 'chillum' or 'huqqa' which is also a concern as smokeless tobacco use is increasingly associated with maternal cigarette smoking [22-27]. Additionally, tobacco, either chewed, applied orally, or smoked actively or passively, increases stillbirths by nearly three folds, reduces birth weight by 100-400 gm, significantly increases placental weight and is also associated with high fetal mortality [24]. The NHS of Pakistan reported that 31% of pregnant women who had ever tried cigarette smoking had transitioned to regular use and among these regular users, 76.9% admitted that they are currently smoking [5]. Notably, the majority (92%) of these women reported that smoking cigarettes or other tobacco products was permitted in their home. About half of the women reported that they and their young children were frequently or always exposed to indoor tobacco smoke. This has important implications as women and children are the most vulnerable in terms of experiencing the adverse effects of tobacco use. Passive smoking has been found to be associated with preterm birth [28 29] and LBW [30] among pregnant women.

There are other risk factors that may also be associated with such adverse pregnancy outcomes and could also be potential confounders of the association between tobacco use and birth outcomes. Malnourishment among females living in resource poor settings predisposes them to anemia and infections due to inadequate food intake [31 32]. Studies from Zimbabwe and Bangladesh reported that maternal mid arm circumference was strongly related with LBW [33]and preterm birth [34]. Moreover, females undergoing antenatal complications are at an increased risk of adverse pregnancy outcomes [35].

Another important factor is indoor air pollution (IAP) from solid fuel use which has been linked to acute lower respiratory infections in children and adverse pregnancy outcomes. Systematic reviews with meta-analyses have reported the association between IAP and increased risk of

LBW and stillbirth [36]. Additional maternal risk factors such as primiparity, poor socio economic status, multiple gestations, premature rupture of membranes, hypertension and under-nutrition can also contribute to adverse pregnancy outcomes [37 38].

The majority of studies conducted in Pakistan on tobacco use have either been cross sectional surveys [5] or have focused primarily on school children [39] and adolescents [40 41]. Very few studies have focused on pregnant women and tobacco consumption [5]. Awareness about tobacco use and its effect on women's health especially during pregnancy is lacking in Pakistan. Smoking and smokeless tobacco use among women is given low priority in public health programs in Pakistan and scant attention is given to this issue by media. Even the public health messaging on media is focused on male members of the society and discussion of second hand smoke is limited. To our knowledge, this is the first case control study from Pakistan to identify the effects of maternal tobacco consumption and other factors during pregnancy on birth outcomes and obstetric complications.

MATERIAL AND METHODS

The study was designed as a multicenter hospital based case control study in Karachi, Pakistan. Karachi is the largest metropolitan city of Pakistan with a population estimated to be about 20 million [42]. Study participants were enrolled from four leading maternity hospitals of Karachi (Civil Hospital, Jinnah Postgraduate Medical College Hospital, Lyari General Hospital and Sobhraj Maternity Hospital) from March to December, 2011. The study population comprised of all pregnant women aged 16 to 45 years, coming to the selected hospitals from different ethnic, social, cultural and economic groups.

Inclusion Criteria

Cases

Cases were pregnant women with singleton pregnancy presenting with the following outcomes:

a) LBW (< 2.5 kg) babies, still births (Any child delivered after the 28th week of pregnancy who did not breathe afterwards or show any signs of life) and intra uterine deaths (fetus dies in uterus before the labor starts).b) Cesarean section due to Fetal distress: (decreased heart rate <100 beats/min and /or passing meconium during labour) c) Antepartum hemorrhage: (bleeding from the vagina occurring at any time after 28th week of pregnancy and before the birth of the child) d) Abruptio placentae: Hemorrhage due to the partial separation of a placenta normally situated on the upper segment of the uterus e) Placenta praevia: Hemorrhage due to partial separation of a placenta abnormally situated on the lower segment of the uterus f) Preterm labor (labor occurring before the 37th week of pregnancy) g) Abnormal uterine action-Prolonged labour: Failed indication (Delay in labor) due to primary uterine hypotonia in which contractions are weak, short and infrequent.

Controls

Controls were women with singleton term deliveries (37-40 weeks) having the following outcomes:

a) Normal Vaginal deliveries with or without episiotomy b) Normal vaginal assisted (forceps or vacuum) deliveries c) Cesarean sections due to cephalo-pelvic disproportion (obstructed labor), malpresentation of fetus and cord around the neck.

Exclusion Criteria

Women with history of diabetes mellitus, gestational diabetes, hypertension before pregnancy, pre-eclampsia, eclampsia, severe anemia (Hemoglobin <8 mg), cardiovascular diseases (valvular

defects, congestive failures etc), chronic obstructive pulmonary disease, renal diseases, active infections (tuberculosis, hepatitis), epilepsy and severe complications in previous pregnancies and multiple births were excluded from the study.

Sample size and Sampling strategy

Each hospital was treated as a stratum, cases and controls were selected randomly from hospitals. To determine sample size, a value of α =0.05 and β=0.2 was specified and an OR of 1.6 was assumed. In Pakistan, approximately 25% of newborns have LBW [43]. Using these values, the required sample size was 1275 individuals with a design effect of 1.1[43] and 10% non-response rate. A case to control ratio of 1:3 was used. A proportionate stratification technique was used to draw the samples from each hospital. In this technique, sample size of each stratum is proportionate to the population size of the stratum. The average number of delivered ladies was calculated in all five hospitals. Proportions (weight) of delivered ladies in each hospital were calculated by taking ratio between number of delivered ladies in each hospital and total number of delivered ladies in all five hospitals. The total number of deliveries was multiplied by calculated proportions (weight) of each hospital.

Enrollment of cases and controls

Trained data collectors interviewed mothers in obstetrics and gynecology wards of the selected hospitals within 48 hours of delivery. Based on the case and control definition, the registers of the wards were searched for study participants who were selected randomly and then approached for interviews after receiving their consent.

Definition of tobacco users

All pregnant women who had regularly used tobacco products (smoke and smokeless) for the past six-months [44] at least 3 times per week were considered as tobacco users.

Data Collection procedure/ Tool

One research coordinator and three female data collectors were hired for data collection who were trained by the Principal Investigator. Data collectors checked hospital records daily to obtain information about the expected number of women delivering babies on the day of visit to the hospitals. Field team visited the normal vaginal delivery room, recovery room and intensive care unit on a daily basis to gather the required information. After selection, an informed consent was taken from each woman. Study participants were explained the purpose of the study and any queries were addressed. Although this was not an intervention study, after the interview, data collectors provided information to subjects about ill effects of tobacco use during pregnancy to make them aware of the health issues related with tobacco use.

Questionnaire

The questionnaire was developed in English and then translated into Urdu. The questionnaire contained questions regarding maternal socio-demographic information, previous and current obstetric characteristics, physical condition and tobacco consumption in any form during pregnancy. The last part of questionnaire focused on the main outcome of the study; Apgar score (< 7), weight of newborn, caesarean section, preterm birth and stillbirth.

Ethical consideration

Ethical approval for the study was obtained from the Aga Khan University's Ethical Review Committee. Written consent was obtained from all the hospitals' administration and individuals before an interview. Every precaution was taken to respect the privacy of subject.

Data editing and entry

The principal investigator and the data collectors edited filled questionnaires on a daily basis in the field and office. Data were double entered by two data entry operators in Epi-info version 6.04 [45].

Statistical analysis

Analyses were performed using STATA version 12.0. Descriptive analysis was carried out by calculating mean and standard deviation for continuous variables, and proportions for categorical variables. Logistic regression analysis was performed to study the associations between tobacco use and other factors and adverse pregnancy outcomes [46]. Crude odds ratio (OR) and their 95% confidence interval (CIs) were calculated. Those variables with p-value ≤0.25 or biological or social importance were selected for multiple logistic regression analysis [46]. Adjusted odds ratios (AOR) and their 95% CIs were obtained from multiple logistic regression model. All potential confounders and biologically plausible interactions were evaluated.

RESULTS

A total of 1275 women (312 cases and 963 controls) with singleton births were recruited for this study. The median duration of marriage were 3 years (IQR = 1.0-7.0 years) among cases and 5 years (IQR= 3.0-9.0 years) among controls with median gravidity of 2 children in both groups. About 42.3% cases and 24.4% controls were exposed to tobacco. Exposure to tobacco between case (with adverse birth outcome) and controls was found to be significantly different (Table 1). Cases included 312 participants consisting of 62 preterm, 15 still births, 9 intrauterine deaths, and 137 with weight less than 2.5 kg. The average weight of baby among cases was 2.5 Kg (SD = 0.6 Kg) and there were a total of 216 babies delivered by caesarian section. The control group comprised of 963 women without any of these conditions (Table 2).

Binary logistic regression analysis showed a significant association between exposure to tobacco [smoke or smokeless] and adverse pregnancy outcome at the univariable level (OR: 2.27; 95% CI: 1.73-2.97). The estimated odds ratios of women who had history of any illness or previous adverse pregnancy or birth outcome were significantly higher among cases compared to controls (Table 3).

Age of women was also associated with adverse pregnancy outcome. For educational level, family history of illness, and gestational age, there were no significant difference found between cases and controls. Cases were more likely to cook in kitchens without a slit/window (a proxy indicator for indoor pollution) (OR=1.7; 95% CI: 1.1 -2.8) as compared to controls.

The final multiple logistic regression analysis indicated that the odds of exposure to tobacco use among cases were 2.24 times compared to controls (OR: 2.24; 95% CI: 1.56-3.23) after adjusting for other variables in the model. Age (adjusted OR= 1.03; 95% CI: 1.0-1.1), no slits in the kitchen (adjusted OR: 1.90; 95% CI: 1.05-3.43), gravidity (adjusted OR= 0.83; 95% CI: 0.73-

0.93), non-booked hospital cases (adjusted OR= 1.87; 95% CI: 1.38-2.74), history of still birth (adjusted OR= 4.06; 95% CI: 2.36-6.97), miscarriages (adjusted OR= 1.91; 95% CI: 1.27-2.85) and history of preterm delivery(adjusted OR= 6.04; 95% CI: 2.52- 14.48) were significantly associated with being a case as compared to control (Table 4).

DISCUSSION

In our study tobacco (smoked or smokeless) use was significantly associated with adverse pregnancy and obstetrics complications. Previous epidemiological studies have also reported that tobacco use [47 14 48 49] is associated with preterm delivery. Smoking during pregnancy releases carbon monoxide and/or nicotine which induce fetal hypoxia. Fetal haemoglobin has a higher affinity for carbon monoxide than adult haemoglobin and the impact on the fetus is more severe than on the mother [50] Therefore, counselling of pregnant females about the detrimental effects of tobacco use is warranted.

Our study also reported that having no slits or windows in the kitchen; a proxy indicator for IAP resulted in an increased risk of adverse birth outcomes. IAP is one of the major risk factors for pneumonia related morbidity, LBW and death in children worldwide [51]. In Pakistan, the use of wood for cooking fuel is common (>53%) and overall biomass use including wood, crop residues, and animal dung is >70% [51]. Inhalation of smoke or particulate matter during cooking could have an adverse effect on pregnant women [36]. Research from developing countries have described an association between the use of biomass fuels in open fires for cooking and LBW [52] [53] preterm birth [54] and SGA [55]. Reports from surveys in India have shown an association between the use of biomass cooking fuel [56] and stillbirths and LBW[57], findings which are consistent with our study. Therefore, in our context, awareness about IAP should be created especially among

women as they are more likely to cook using biomass fuels whereas a general awareness campaign about IAP can be implemented through media.

In our study, we found that increasing age of the female was significantly associated with adverse pregnancy outcomes, a finding supported by several studies [58-60]. Our study also identified women having previous history of stillbirth, miscarriage and preterm deliveries to be associated with adverse birth outcomes which is consistent with previous research [61].

We found that the cases were less likely to be booked at the hospital as compared to controls. These cases had a history of previous pregnancy complications predisposing them to higher risk of adverse pregnancy outcomes. Plausibly, non-booking of women in hospitals especially with previous history of adverse birth outcomes is an indicator of lack of awareness of future pregnancy complications and could be a function of scarce resources. Therefore, creating awareness among these vulnerable women and frequent ante-natal visits are essential to prevent such complications.

Another important finding was that blood transfusion was significantly associated with adverse pregnancy outcomes. Anemia, a proxy indicator for blood transfusion is usually detected at the first antenatal visit. If anemia persists the fetus may not receive enough oxygen, and the risk of preterm is increased. In our study cases may be unaware of their hemoglobin status and may have been severely anemic because of missed pre-natal checkups, therefore, at the time of delivery may be in desperate need of blood transfusion which could have led to the adverse pregnancy outcomes. However, in our study we were unable to retrieve information regarding the hemoglobin levels of the pregnant female. Gravidity showed an inverse association with adverse birth outcomes which needs to be explored further to determine if women who were previously pregnant are more likely to take better care of themselves during future pregnancies.

Strengths of our study included a robust method of recruitment to reduce misclassification of the outcome and being a multicenter study catering to patients from different ethnic and socioeconomic backgrounds, thereby enhancing generalizability of our results. Most of the information in our study was self-reported, therefore, it was prone to reporting bias [62]. However, any such bias is likely to be a non-differential misclassification, and the potential effect might be underestimation of the association because such biases tend to distort the associations towards null. So the potential effect of tobacco and other risk factors may even be more pronounced on adverse pregnancy outcomes, given that we assume that such misclassification exist in our study. Furthermore, we were not able to obtain serum cotinine levels which would have been a better measure. Although the effects of smoking, smokeless tobacco use and secondhand smoke are different on birth outcomes, we were unable to construct separate models for each exposure due to small numbers of smokers in our sample.

This study identified tobacco use as a very important risk factor for adverse birth outcomes in Pakistan. Commonly, tobacco use is either associated with respiratory disorders or oral cancers in Pakistan and is not associated with adverse birth outcomes. Our study highlights this issue and advocates for awareness among pregnant women and general population about the ill effects of tobacco use during pregnancy. Stakeholders in tobacco control including government, NGO's and health professionals should be made aware of this issue and should be engaged in order to prevent adverse outcomes in pregnant women. We also found previous history of birth complications and non booking in hospital as additional important predictors which suggest gaps in awareness of mothers about tobacco use during pregnancy. From a health system perspective it may indicate that women are either not accessing the health system for ante-natal care or are

doing so very infrequently. We also found that improper ventilation (no slits in the kitchen) used as a proxy indicator for IAP as one of the predictors for adverse birth outcomes. Preventative measures either in the form of reducing the use of biomass fuels or reducing the time spent in kitchen during pregnancy could be warranted. However, future research is required on this issue to evaluate the feasibility of these measures and also to come up with a contextually relevant intervention.

CONCLUSION

Our study underscores the importance of ante-natal care and health education about the effects of tobacco use and other factors during pregnancy which may lead to adverse pregnancy outcomes. We recommend engagement of stakeholders in tobacco control; for providing health education and awareness, incorporating tobacco use among women in the tobacco control policy and for designing interventions for tobacco use cessation among women. Interventions aimed at improving pre-natal care and health education during the antenatal period could be immediate measures which might help in reducing the burden of tobacco use and also prevent such adverse pregnancy related events.

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Author's note

SR contributed to analysis, interpretation, manuscript drafting and reviewing. ZAB and NZ were responsible for manuscript writing, and reviewing the paper. SW helped in data cleaning, management, and analysis. KS contributed to manuscript drafting and reviewing the paper. All authors saw and approved the final version of manuscript.

Competing Interests

None declared.

Data Sharing Statement

No additional unpublished data is available from the study. The data of this study is with the first author of the manuscript.

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Table 1. Characteristics of cases and controls presenting at selected hospitals in Karachi, Pakistan

Characteristics		Cases n (%)	Controls n (%)
Age of mother (Years)			
Mean (S.D)		25.3 (4.8)	26.0 (4.6)
Mother tongue of respondent			
Urdu		168 (53.8)	492 (51.1)
Sindhi		31(9.9)	88 (9.1)
Punjabi		20 (6.4)	79 (8.2)
Balochi		28 (9.0)	99 (10.3)
Pashto		31 (9.9)	111 (11.5)
Others		34 (10.9)	94 (9.8)
Educational level			
No formal education		114 (36.5)	353 (36.7)
Primary & secondary		160 (51.3)	519 (53.9)
Intermediate		26 (8.3)	66 (6.9)
Graduate & post graduate		12 (3.8)	25 (2.6)
Religion			
Muslim		302 (96.8)	937 (97.3)
Christian		1 (0.3)	8 (0.8)
Hindu		9 (2.9)	18 (1.9)
Family system			
Nuclear		106 (34.0)	356 (37.0)
Joint		206 (66.0)	607 (63.0)
Nature of house			
Kachchaa		14 (4.5)	21 (2.2)
Pakka		298 (95.5)	942 (97.8)
Work currently			
No		307 (98.4)	952 (98.9)
Yes		5 (1.6)	11 (1.1)
Gravidity	Med (IQR)	2.0 (1.0 – 3.0)	2.0 (3.0 - 4.0)
Years of marriage	Med (IQR)	3.0 (1.0 - 7.0)	5.0 (3.0 – 9.0)
No. of antenatal care visits			
Mean (S.D		6.6 (3.6)	6.5 (3.2)
Ever domestic violence			
No		306 (98.1)	947 (98.3)
Yes		6 (1.9)	16 (1.7)
Gestational age when fetal movement started (Weeks)			
Mean (S.D)		20.7 (2.3)	20.7 (2.2)

Table 1. Continued.

Complication during current pregnancy		
No	192 (61.5)	765 (79.4)
Yes	120 (38.5)	198 (20.6)
Immunization done during this pregnancy		
No	65 (20.8)	216 (22.4)
Yes	247 (79.2)	747 (77.6)
Ultrasound done during this pregnancy		
No	8 (2.6)	19 (2.0)
Yes	304 (97.4)	944 (98.0)
Duration between water break and delivery of baby (Hours) Med(IQR)	13.0 (6.0 – 36.0)	6.0 (2.0 – 14.0)
Material/fuel use for cooking		
Gas	291 (93.3)	905 (94.0)
Wwood & others	21(6.7)	58 (6.0)
Slits/window in the kitchen		
No	29 (9.3)	54 (5.6)
Yes	283 (90.7)	909 (94.4)
Slits/window in the house		
No	12 (3.8)	26 (2.7)
Yes	300 (96.2)	937 (97.3)
Exhaust fan in kitchen		
No	277 (88.8)	834 (86.6)
Yes	35 (11.2)	129 (13.4)
Average time spend in kitchen while stove burning (hours) Mean(S.D)	1.9 (0.9)	1.9 (0.9)
Exposed to tobacco		
No	180 (57.7)	728 (75.6)
Yes	132 (42.3)	235 (24.4)

Table 2: Distribution of adverse pregnancy outcomes and obstetric complications among cases and controls at selected hospitals in Karachi, Pakistan

Outcome	Cases n (%)	Controls n (%)
Preterm delivery		
No	250 (80.1)	963 (100)
Yes	62 (19.8)	-
Caesarian section		
No	96 (30.8)	596 (61.9)
Yes	216 (69.2)	367 (38.1)
Status of baby at birth		
Alive	288 (92.3)	963 (100.0)
IUD	9 (2.9)	-
Still birth	15 (4.8)	-
Birth weight of baby (kg)		
Mean(S.D)	2.5 (0.6)	3.0 (0.4)

Table 3: Univariate analysis of factors associated with adverse birth outcomes and obstetric complications among cases and controls at selected hospitals in Karachi, Pakistan

Characteristics	Controls n = 963	Cases n =312	Crude Odds ratio (OR)	95% CI
Age of Mother (Years)				
Mean (SD)	26.0 (4.6)	25.3 (4.8)	0.96	(0.90-1.0)
Educational Level				
No Formal education	353 (36.7)	114 (36.5)	1	-
Primary & Secondary	519 (53.9)	160 (51.3)	0.95	(0.73-1.25)
Intermediate	66 (6.9)	26 (8.3)	1.22	(0.74-2.01)
Graduate and Post graduate	25 (2.6)	12 (3.8)	1.49	(0.72-3.05)
Nature of house				
Kachchaa	21 (2.2)	14 (4.5)	1	-
Pakka	942 (97.8)	298 (95.5)	2.11	(1.10- 4.21)
Mother's history of illness				
No	959 (99.6)	305 (97.8)	1	-
Yes	4 (0.4)	7 (2.2)	5.50	(1.60- 18.92)
Family history of illness				
No	556 (57.7)	191(61.2)	1	-
Yes	407 (42.3)	121(38.8)	0.86	(0.72-1.10)
Years of marriage Mean(S.D)	6.1 (5.5)	4.6 (4.6)	0.90	(0.91- 1.00)
Gravidity Mean(S.D)	3.1 (0.1)	2.4 (0.1)	0.82	(0.80-0.91)
History of miscarriage				
No	565 (74.0)	110 (64.0)	1	-
Yes	198 (26.0)	62 (36.0)	1.61	(1.13-2.31)
History of preterm delivery				
No	752 (98.6)	158 (91.9)	1	-
Yes	11(1.4)	14 (8.1)	6.00	(2.71-13.60)
History of still birth				
No	718 (94.1)	142 (82.6)	1	-
Yes	45 (5.9)	30 (17.4)	3.34	(2.13-5.52)
Complication during previous pregnancy				
No	855 (88.8)	261 (83.7)	1	-
Yes	108 (11.2)	51 (16.3)	1.52	(1.10-2.21)

Table 3. Continued.

Booked in the hospital				
Yes	732 (76.0)	204 (65.4)	1	
No	231 (24.0)	108 (34.6)	1.70	(1.32-2.20)
Gestational age when fetal movement started (Weeks)				
Mean(S.E)	20.7 (0.1)	20.7 (0.1)	0.99	(0.94 -1.11)
No. of antenatal care visits	6.5 (0.1)	6.6 (0.2)	1.02	(0.99-1.04)
Micturition problem during pregnancy				
No	793 (82.3)	229 (73.4)	1	
Yes	170 (17.7)	83 (26.6)	1.71	(1.33-2.30)
Taken folic acid tablets				
No	611 (63.4)	199 (63.8)	1	
Yes	352 (36.6)	113 (36.2)	1.02	(0.81-1.30)
Complication during current pregnancy				
No	765 (79.4)	192 (61.5)	1	
Yes	198 (20.6)	120 (38.5)	2.40	(1.80-3.22)
Blood transfusion done				
No	914 (94.9)	286 (91.7)	1	
Yes	49 (5.1)	26 (8.3)	1.70	(1.0-2.80)
Duration between water break and delivery of baby (Hours)				
Mean(S.E)	12.3 (0.7)	27.8 (4.6)	1.03	(1.02-1.03)
Slits/window in the kitchen				
Yes	909 (94.4)	283 (90.7)	1	
No	54 (5.6)	29 (9.3)	1.72	(1.11-2.76)
Exposed to tobacco				
No	728 (75.6)	180 (57.7)	1	
Yes	235 (24.4)	132 (42.3)	2.27	(1.73 -2.97)

Table 4. Multivariate analysis of factors associated with adverse birth outcomes & obstetric complications among cases and controls at selected hospitals in Karachi, Pakistan

Characteristics	Adjusted odds ratio	95 % C.I
Exposure to tobacco smoke		
No	1	
Yes	2.24	(1.56-3.23)
Gravidity	0.83	(0.73-0.93)
Age of mother	1.03	(1.0-1.10)
Booked in hospital		
Yes	1	
No	1.87	(1.38-2.74)
History of Preterm births		
No	1	
Yes	6.04	(2.52- 14.48)
History of miscarriage		
No	1	
Yes	1.91	(1.27 – 2.85)
History of still birth		
No	1	
Yes	4.06	(2.36 – 6.97)
Slit/window in kitchen		
Yes	1	
No	1.90	(1.05 – 3.43)
Blood transfusion done		
No	1	
Yes	3.06	(1.68 – 5.57)

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract √
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found √
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported √
Objectives	3	State specific objectives, including any prespecified hypotheses √
Methods		
Study design	4	Present key elements of study design early in the paper √
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection √
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls √
		(*b*) For matched studies, give matching criteria and the number of controls per case **NA**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable √
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group √
Bias	9	Describe any efforts to address potential sources of bias √
Study size	10	Explain how the study size was arrived at √
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why √
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding √
		(*b*) Describe any methods used to examine subgroups and interactions √
		(*c*) Explain how missing data were addressed NA
		(*d*) If applicable, explain how matching of cases and controls was addressed **NA**
		(*e*) Describe any sensitivity analyses **NA**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed √
		(b) Give reasons for non-participation at each stage * **No reasons**
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders √
		(b) Indicate number of participants with missing data for each variable of interest NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure √
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included √

	(*b*) Report category boundaries when continuous variables were categorized **NA**
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **NA**

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **NA**
Discussion		
Key results	18	Summarise key results with reference to study objectives √
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias √
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence √
Generalisability	21	Discuss the generalisability (external validity) of the study results *
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based √

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Association of Tobacco Use And Other Determinants with Pregnancy Outcomes: A Multi-center Hospital Based Case Control Study in Karachi, Pakistan

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Abstract

Objectives: The study aimed to identify the effects of maternal tobacco consumption during pregnancy and other factors on birth outcomes and obstetric complications in Karachi, Pakistan.

Design: A multi-center hospital based case control study.

Setting: Four leading maternity hospitals of Karachi.

Participants: A random sample of 1275 women coming to the gynecology & obstetric department of selected hospitals for delivery was interviewed within 48 hours of delivery from wards. Cases were women with adverse birth outcomes and obstetric complications while controls were women with who had normal uncomplicated delivery.

Primary and secondary outcome measures: Adverse birth outcomes (preterm delivery, low birth weight, still birth, low APGAR score) and obstetric complications (antepartum hemorrhage, cesarean section etc.)

Results: Final multiple logistic regression analysis revealed that with every one year increase in age the odds of being a case was 1.03 times as compared to being a control. Tobacco use (adjusted OR (aOR) : 2.24; 95% Confidence Interval (CI): 1.56-3.23) , having no slits in the kitchen (proxy indicator for indoor air pollution) (aOR= 1.90; 95% CI: 1.05 – 3.43), gravidity (aOR= 0.83; 95% CI: 0.73-0.93), non-booked hospital cases (aOR= 1.87; 95% CI: 1.38-2.74), history of still birth (aOR= 4.06; 95% CI: 2.36 – 6.97), miscarriages (aOR= 1.91; 95% CI: 1.27 – 2.85) and preterm delivery (aOR= 6.04; 95% CI: 2.52- 14.48) were significantly associated with being a case as compared to control.

Conclusions:

This study suggests that women who had adverse pregnancy outcomes were more likely to have

exposure to tobacco, previous history of adverse birth outcomes and were non booked cases. Engagement of stakeholders in tobacco control for; providing health education, incorporating tobacco use in women in the tobacco control policy and designing interventions for tobacco use cessation is warranted. Pre-natal care and health education might help in preventing such adverse events.

Keywords: Pregnancy outcomes**,** Maternal tobacco use, , other risk factors

Strengths and Limitations of this study

• Our study included a robust method of recruitment to reduce classification of the outcome.

• Being a multicenter hospital based study catering to patients from different ethnic and socioeconomic backgrounds indicates that our results can be generalized.

• One of the limitations of this study was that most of the information was self-reported, therefore, it was prone to reporting bias. However, we had given extensive training to our data collectors to retrieve participant's information as accurately as possible. Numerous studies have shown that self-reported smoking is reliable method of gathering information

• Ideally, serum cotinine levels would have been a better measure; however, it was not possible to obtain blood samples in our study

INTRODUCTION

Low birth weight (LBW) of the infant is a challenging multifaceted public health problem as. It varies from 4.5% in most developed countries to almost 50% in some of the least developed countries [1] .The prevalence of LBW is high in developing countries (18.5 %), with the highest prevalence in South Asia (27 %) including Pakistan [2] and India [1]. Still birth is another important adverse birth outcome. Globally, 3.9 million stillbirths are reported, and unfortunately 97% of them are occurring in the developing world [3].

There are a number of risk factors that may be associated with adverse birth outcomes and obstetric complications. Among them, tobacco use is a major public health problem globally. According to the World Health Organization, there are about one billion smokers worldwide [4]. Smoking prevalence among women varies markedly across countries; it is 7% in developing countries and 24% in developed countries [5]. Tobacco use is common in Pakistan; about 34% of men and 12.5% of women use different forms of tobacco regularly [5]. Notably, 3.2 % of pregnant women had ever been a regular cigarette smoker in Pakistan [6]. Women who smoke cigarettes have higher rate of gynaecological complications [7] and decreased fertility potential [8-10]. Smoking increases the level of nicotine and carbon monoxide in the blood which causes serious complications including increased rate of spontaneous abortion [11], premature delivery [11 12] low birth weight [11 13 14] placenta praevia, bleeding during pregnancy, premature rupture of membranes and stillbirths [15-17]. Other adverse outcomes include Small for Gestational Age (SGA) babies [13 18] miscarriages [19], lipid abnormalities [20], increased risk for hypertension, and gestational diabetes [21].

Another important aspect is the increasing use of alternative forms of tobacco. According to the National Health Survey (NHS) of Pakistan, nearly 10% of females aged 25-64 years reported

regular use of chewing tobacco or snuff and over 7% of women smoked 'chillum' or 'huqqa' which is also a concern as smokeless tobacco use is increasingly associated with maternal cigarette smoking [22-27]. Additionally, tobacco, either chewed, applied orally, or smoked actively or passively, increases stillbirths by nearly three folds, reduces birth weight by 100-400 gm, significantly increases placental weight and is also associated with high fetal mortality [24]. The NHS of Pakistan reported that 31% of pregnant women who had ever tried cigarette smoking had transitioned to regular use and among these regular users, 76.9% admitted that they are currently smoking [5]. Notably, the majority (92%) of these women reported that smoking cigarettes or other tobacco products was permitted in their home. About half of the women reported that they and their young children were frequently or always exposed to indoor tobacco smoke. This has important implications as women and children are the most vulnerable in terms of experiencing the adverse effects of tobacco use. Secondhand smoke has been found to be associated with preterm birth [28 29] and LBW [30] among pregnant women.

There are other risk factors that may also be associated with such adverse pregnancy outcomes and could also be potential confounders of the association between tobacco use and birth outcomes. Malnourishment among females living in resource poor settings predisposes them to anemia and infections due to inadequate food intake [31 32]. Studies from Zimbabwe and Bangladesh reported that maternal mid arm circumference was strongly related with LBW [33]and preterm birth [34]. Moreover, females undergoing antenatal complications are at an increased risk of adverse pregnancy outcomes [35].

Another important factor is indoor air pollution (IAP) from solid fuel use which has been linked to acute lower respiratory infections in children and adverse pregnancy outcomes. Systematic reviews with meta-analyses have reported the association between IAP and increased risk of

LBW and stillbirth [36]. Additional maternal risk factors such as primiparity, poor socio economic status, multiple gestations, premature rupture of membranes, hypertension and under-nutrition can also contribute to adverse pregnancy outcomes [37 38].

The majority of studies conducted in Pakistan on tobacco use have either been cross sectional surveys [5] or have focused primarily on school children [39] and adolescents [40 41]. Very few studies have focused on pregnant women and tobacco consumption [5]. Awareness about tobacco use and its effect on women's health especially during pregnancy is lacking in Pakistan. Smoking and smokeless tobacco use among women is given low priority in public health programs in Pakistan and scant attention is given to this issue by media. Even the public health messaging on media is focused on male members of the society and discussion of second hand smoke is limited. To our knowledge, this is the first case control study from Pakistan to identify the effects of maternal tobacco consumption and other factors during pregnancy on birth outcomes and obstetric complications.

MATERIAL AND METHODS

The study was designed as a multicenter hospital based case control study in Karachi, Pakistan. Karachi is the largest metropolitan city of Pakistan with a population estimated to be about 20 million [42]. Study participants were enrolled from four leading maternity hospitals of Karachi (Civil Hospital, Jinnah Postgraduate Medical College Hospital, Lyari General Hospital and Sobhraj Maternity Hospital) from March to December, 2011. The study population comprised of all pregnant women aged 16 to 45 years, coming to the selected hospitals from different ethnic, social, cultural and economic groups.

Inclusion Criteria

Cases

Cases were pregnant women with singleton pregnancy presenting with the following outcomes:

a) LBW (< 2.5 kg) babies, b) still births (Any child delivered after the 28th week of pregnancy who did not breathe afterwards or show any signs of life) and c) intra uterine deaths (fetus dies in uterus before the labor starts).d) Cesarean section due to Fetal distress: (decreased heart rate <100 beats/min and /or passing meconium during labour) e) Antepartum hemorrhage: (bleeding from the vagina occurring at any time after 28th week of pregnancy and before the birth of the child) f) Abruptio placentae: Hemorrhage due to the partial separation of a placenta normally situated on the upper segment of the uterus g) Placenta praevia: Hemorrhage due to partial separation of a placenta abnormally situated on the lower segment of the uterus h) Preterm labor (labor occurring before the 37th week of pregnancy) i) Abnormal uterine action-Prolonged labour: Failed indication (Delay in labor) due to primary uterine hypotonia in which contractions are weak, short and infrequent.

Controls

Controls were women with singleton term deliveries (37-40 weeks) having the following outcomes:

a) Normal Vaginal deliveries with or without episiotomy b) Normal vaginal assisted (forceps or vacuum) deliveries c) Cesarean sections due to cephalo-pelvic disproportion (obstructed labor), malpresentation of fetus and cord around the neck.

Exclusion Criteria

Women with history of diabetes mellitus, gestational diabetes, hypertension before pregnancy, pre-eclampsia, eclampsia, severe anemia (Hemoglobin <8 mg), cardiovascular diseases (valvular

defects, congestive failures etc), chronic obstructive pulmonary disease, renal diseases, active infections (tuberculosis, hepatitis), epilepsy and severe complications in previous pregnancies and multiple births were excluded from the study.

Sample size and Sampling strategy

Each hospital was treated as a stratum, cases and controls were selected randomly from hospitals. To determine sample size, a value of α =0.05 and β=0.2 was specified and an OR of 1.6 was assumed. In Pakistan, approximately 25% of newborns have LBW [43]. Using these values, the required sample size was 1275 individuals with a design effect of 1.1[43] and 10% non-response rate. A case to control ratio of 1:3 was used. A proportionate stratification technique was used to draw the samples from each hospital. In this technique, sample size of each stratum is proportionate to the population size of the stratum. The average number of delivered ladies was calculated in all five hospitals. Proportions (weight) of delivered ladies in each hospital were calculated by taking ratio between number of delivered ladies in each hospital and total number of delivered ladies in all five hospitals. The total number of deliveries was multiplied by calculated proportions (weight) of each hospital.

Enrollment of cases and controls

Trained data collectors interviewed mothers in obstetrics and gynecology wards of the selected hospitals within 48 hours of delivery. Based on the case and control definition, the registers of the wards were searched for study participants who were selected randomly and then approached for interviews after receiving their consent.

Definition of tobacco users

All pregnant women who had regularly used tobacco products (smoke and smokeless) for the past six-months [44] at least 3 times per week were considered as tobacco users.

Data Collection procedure/ Tool

One research coordinator and three female data collectors were hired for data collection who were trained by the Principal Investigator. Data collectors checked hospital records daily to obtain information about the expected number of women delivering babies on the day of visit to the hospitals. Field team visited the normal vaginal delivery room, recovery room and intensive care unit on a daily basis to gather the required information. After selection, an informed consent was taken from each woman. Study participants were explained the purpose of the study and any queries were addressed. Although this was not an intervention study, after the interview, data collectors provided information to subjects about ill effects of tobacco use during pregnancy to make them aware of the health issues related with tobacco use.

Questionnaire

The questionnaire was developed in English and then translated into Urdu. The questionnaire contained questions regarding maternal socio-demographic information, previous and current obstetric characteristics, physical condition and tobacco consumption in any form during pregnancy. The last part of questionnaire focused on the main outcome of the study; Apgar score (< 7), weight of newborn, caesarean section, preterm birth and stillbirth.

Ethical consideration

Ethical approval for the study was obtained from the Aga Khan University's Ethical Review Committee. Written consent was obtained from all the hospitals' administration and individuals before an interview. Every precaution was taken to respect the privacy of subject.

Data editing and entry

The principal investigator and the data collectors edited filled questionnaires on a daily basis in the field and office. Data were double entered by two data entry operators in Epi-info version 6.04 [45].

Statistical analysis

Analyses were performed using STATA version 12.0. Descriptive analysis was carried out by calculating mean and standard deviation for continuous variables, and proportions for categorical variables. Logistic regression analysis was performed to study the associations between tobacco use and other factors and adverse pregnancy outcomes [46]. Crude odds ratio (OR) and their 95% confidence interval (CIs) were calculated. Those variables with p-value ≤0.25 or biological or social importance were selected for multiple logistic regression analysis [46]. Adjusted odds ratios (AOR) and their 95% CIs were obtained from multiple logistic regression model. All potential confounders and biologically plausible interactions were evaluated.

RESULTS

A total of 1275 women (312 cases and 963 controls) with singleton births were recruited for this study. The median duration of marriage were 3 years (IQR = 1.0-7.0 years) among cases and 5 years (IQR= 3.0-9.0 years) among controls with median gravidity of 2 children in both groups. Proportion of tobacco use was 42.3% among cases and 24.4% among controls. Tobacco use between case (with adverse birth outcome) and controls was found to be significantly different (Table 1).

Cases included 312 participants consisting of 62 preterm, 15 still births, 9 intrauterine deaths, and 137 with weight less than 2.5 kg. The average weight of baby among cases was 2.5 Kg (SD = 0.6 Kg) and there were a total of 216 babies delivered by caesarian section. The control group comprised of 963 women without any of these conditions (Table 2).

Binary logistic regression analysis showed a significant association between tobacco use [smoke or smokeless] and adverse pregnancy outcome at the univariable level (OR: 2.27; 95% CI: 1.73-2.97). The estimated odds ratios of women who had history of any illness or previous adverse pregnancy or birth outcome were significantly higher among cases compared to controls (Table 3).

Age of women was also associated with adverse pregnancy outcome. For educational level, family history of illness, and gestational age, there were no significant difference found between cases and controls. Cases were more likely to cook in kitchens without a slit/window (a proxy indicator for indoor pollution) (OR=1.7; 95% CI: 1.1 -2.8) as compared to controls.

The final multiple logistic regression analysis indicated that the odds of tobacco use among cases were 2.24 times compared to controls (OR: 2.24; 95% CI: 1.56-3.23) after adjusting for other variables in the model. Age (adjusted OR= 1.03; 95% CI: 1.0-1.1), no slits in the kitchen

(adjusted OR: 1.90; 95% CI: 1.05-3.43), gravidity (adjusted OR= 0.83; 95% CI: 0.73-0.93), non-booked hospital cases (adjusted OR= 1.87; 95% CI: 1.38-2.74), history of still birth (adjusted OR= 4.06; 95% CI: 2.36-6.97), miscarriages (adjusted OR= 1.91; 95% CI: 1.27-2.85) and history of preterm delivery(adjusted OR= 6.04; 95% CI: 2.52- 14.48) were significantly associated with being a case as compared to control (Table 4).

DISCUSSION

In our study tobacco use was significantly associated with adverse pregnancy and obstetrics complications. Previous epidemiological studies have also reported that tobacco use [47 14 48 49] is associated with preterm delivery. Smoking during pregnancy releases carbon monoxide and/or nicotine which induce fetal hypoxia. Fetal haemoglobin has a higher affinity for carbon monoxide than adult haemoglobin and the impact on the fetus is more severe than on the mother [50] Therefore, counselling of pregnant females about the detrimental effects of tobacco use is warranted.

Our study also reported that having no slits or windows in the kitchen; a proxy indicator for IAP resulted in an increased risk of adverse birth outcomes. IAP is one of the major risk factors for pneumonia related morbidity, LBW and death in children worldwide [51]. In Pakistan, the use of wood for cooking fuel is common (>53%) and overall biomass use including wood, crop residues, and animal dung is >70% [51]. Inhalation of smoke or particulate matter during cooking could have an adverse effect on pregnant women [36]. Research from developing countries have described an association between the use of biomass fuels in open fires for cooking and LBW [52] [53] preterm birth [54] and SGA [55]. Reports from surveys in India have shown an association between the use of biomass cooking fuel [56] and stillbirths and LBW[57], findings which are consistent with our study. Therefore, in our context, awareness about IAP should be created especially among

women as they are more likely to cook using biomass fuels whereas a general awareness campaign about IAP can be implemented through media.

In our study, we found that increasing age of the female was significantly associated with adverse pregnancy outcomes, a finding supported by several studies [58-60]. Our study also identified women having previous history of stillbirth, miscarriage and preterm deliveries to be associated with adverse birth outcomes which is consistent with previous research [61].

We found that the cases were less likely to be booked at the hospital as compared to controls. These cases had a history of previous pregnancy complications predisposing them to higher risk of adverse pregnancy outcomes. Plausibly, non-booking of women in hospitals especially with previous history of adverse birth outcomes is an indicator of lack of awareness of future pregnancy complications and could be a function of scarce resources. Therefore, creating awareness among these vulnerable women and frequent ante-natal visits are essential to prevent such complications.

Another important finding was that blood transfusion was significantly associated with adverse pregnancy outcomes. Anemia, a proxy indicator for blood transfusion is usually detected at the first antenatal visit. If anemia persists the fetus may not receive enough oxygen, and the risk of preterm is increased. In our study cases may be unaware of their hemoglobin status and may have been severely anemic because of missed pre-natal checkups, therefore, at the time of delivery may be in desperate need of blood transfusion which could have led to the adverse pregnancy outcomes. However, in our study we were unable to retrieve information regarding the hemoglobin levels of the pregnant female. Gravidity showed an inverse association with adverse birth outcomes which needs to be explored further to determine if women who were previously pregnant are more likely to take better care of themselves during future pregnancies.

Strengths of our study included a robust method of recruitment to reduce misclassification of the outcome and being a multicenter study catering to patients from different ethnic and socioeconomic backgrounds, thereby indicating that our results can be generalized. Most of the information in our study was self-reported, therefore, it was prone to reporting bias [62]. However, any such bias is likely to be a non-differential misclassification, and the potential effect might be underestimation of the association because such biases tend to distort the associations towards null. So the potential effect of tobacco and other risk factors may even be more pronounced on adverse pregnancy outcomes, given that we assume that such misclassification exist in our study. Furthermore, we were not able to obtain serum cotinine levels which would have been a better measure. Although the effects of smoking and smokeless tobacco use are different on birth outcomes, we were unable to construct separate models for each exposure due to small numbers of smokers in our sample.

This study identified tobacco use as a very important risk factor for adverse birth outcomes in Pakistan. Commonly, tobacco use is either associated with respiratory disorders or oral cancers in Pakistan and is not associated with adverse birth outcomes. Our study highlights this issue and advocates for awareness among pregnant women and general population about the ill effects of tobacco use during pregnancy. Stakeholders in tobacco control including government, NGO's and health professionals should be made aware of this issue and should be engaged in order to prevent adverse outcomes in pregnant women. We also found previous history of birth complications and non booking in hospital as additional important predictors which suggest gaps in awareness of mothers about tobacco use during pregnancy. Improper ventilation (no slits in the kitchen) used as a proxy indicator for IAP was another significant predictor for adverse birth

outcomes. Preventative measures either in the form of reducing the use of biomass fuels or reducing the time spent in kitchen during pregnancy could be warranted. However, future research is required on this issue to evaluate the feasibility of these measures and also to come up with a contextually relevant intervention.

CONCLUSION

Our study underscores the importance of ante-natal care and health education about the effects of tobacco use and other factors during pregnancy which may lead to adverse pregnancy outcomes. We recommend engagement of stakeholders in tobacco control; for providing health education and awareness, incorporating tobacco use among women in the tobacco control policy and for designing interventions for tobacco use cessation among women. Interventions aimed at improving pre-natal care and health education during the antenatal period could be immediate measures which might help in reducing the burden of tobacco use and also prevent such adverse pregnancy related events.

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Author's note

SR contributed to analysis, interpretation, manuscript drafting and reviewing. ZAB and NZ were responsible for manuscript writing, and reviewing the paper. SW helped in data cleaning, management, and analysis. KS contributed to manuscript drafting and reviewing the paper. All authors saw and approved the final version of manuscript.

Competing Interests

None declared.

Data Sharing Statement

No additional unpublished data is available from the study. The data of this study is with the first author of the manuscript.

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Table 1. Characteristics of cases and controls presenting at selected hospitals in Karachi, Pakistan

Characteristics	Cases n (%)	Controls n (%)
Age of mother (Years)		
Mean (S.D)	25.3 (4.8)	26.0 (4.6)
Mother tongue of respondent		
Urdu	168 (53.8)	492 (51.1)
Sindhi	31(9.9)	88 (9.1)
Punjabi	20 (6.4)	79 (8.2)
Balochi	28 (9.0)	99 (10.3)
Pashto	31 (9.9)	111 (11.5)
Others	34 (10.9)	94 (9.8)
Educational level		
No formal education	114 (36.5)	353 (36.7)
Primary & secondary	160 (51.3)	519 (53.9)
Intermediate	26 (8.3)	66 (6.9)
Graduate & post graduate	12 (3.8)	25 (2.6)
Religion		
Muslim	302 (96.8)	937 (97.3)
Christian	1 (0.3)	8 (0.8)
Hindu	9 (2.9)	18 (1.9)
Family system		
Nuclear	106 (34.0)	356 (37.0)
Joint	206 (66.0)	607 (63.0)
Nature of house		
Kachchaa (made by mud and wood)	14 (4.5)	21 (2.2)
Pakka (made by bricks and cement)	298 (95.5)	942 (97.8)
Work currently		
No	307 (98.4)	952 (98.9)
Yes	5 (1.6)	11 (1.1)
Gravidity Med (IQR)	2.0 (1.0 – 3.0)	2.0 (3.0 - 4.0)
Years of marriage Med (IQR)	3.0 (1.0 - 7.0)	5.0 (3.0 – 9.0)
No. of antenatal care visits		
Mean (S.D	6.6 (3.6)	6.5 (3.2)
Ever domestic violence		
No	306 (98.1)	947 (98.3)
Yes	6 (1.9)	16 (1.7)
Gestational age when fetal movement started (Weeks)		
Mean (S.D)	20.7 (2.3)	20.7 (2.2)

Table 1. Continued.

Complication during current pregnancy		
No	192 (61.5)	765 (79.4)
Yes	120 (38.5)	198 (20.6)
Immunization done during this pregnancy		
No	65 (20.8)	216 (22.4)
Yes	247 (79.2)	747 (77.6)
Ultrasound done during this pregnancy		
No	8 (2.6)	19 (2.0)
Yes	304 (97.4)	944 (98.0)
Duration between water break and delivery of baby (Hours) Med(IQR)	13.0 (6.0 – 36.0)	6.0 (2.0 – 14.0)
Material/fuel use for cooking		
Gas	291 (93.3)	905 (94.0)
Wwood & others	21(6.7)	58 (6.0)
Slits/window in the kitchen		
No	29 (9.3)	54 (5.6)
Yes	283 (90.7)	909 (94.4)
Slits/window in the house		
No	12 (3.8)	26 (2.7)
Yes	300 (96.2)	937 (97.3)
Exhaust fan in kitchen		
No	277 (88.8)	834 (86.6)
Yes	35 (11.2)	129 (13.4)
Average time spend in kitchen while stove burning (hours) Mean(S.D)	1.9 (0.9)	1.9 (0.9)
Tobacco use		
No	180 (57.7)	728 (75.6)
Yes	132 (42.3)	235 (24.4)

Table 2: Distribution of adverse pregnancy outcomes and obstetric complications among cases and controls at selected hospitals in Karachi, Pakistan

Outcome	Cases n (%)	Controls n (%)
Preterm delivery		
No	250 (80.1)	963 (100)
Yes	62 (19.8)	-
Caesarian section		
No	96 (30.8)	596 (61.9)
Yes	216 (69.2)	367 (38.1)
Status of baby at birth		
Alive	288 (92.3)	963 (100.0)
IUD	9 (2.9)	-
Still birth	15 (4.8)	-
Birth weight of baby (kg)		
Mean(S.D)	2.5 (0.6)	3.0 (0.4)

Table 3: Univariate analysis of factors associated with adverse birth outcomes and obstetric complications among cases and controls at selected hospitals in Karachi, Pakistan

Characteristics	Controls n = 963	Cases n =312	Crude Odds ratio (OR)	95% CI
Age of Mother (Years)				
Mean (SD)	26.0 (4.6)	25.3 (4.8)	0.96	(0.90-1.0)
Educational Level				
No Formal education	353 (36.7)	114 (36.5)	1	-
Primary & Secondary	519 (53.9)	160 (51.3)	0.95	(0.73-1.25)
Intermediate	66 (6.9)	26 (8.3)	1.22	(0.74-2.01)
Graduate and Post graduate	25 (2.6)	12 (3.8)	1.49	(0.72-3.05)
Nature of house				
Kachchaa (made by mud and wood)	21 (2.2)	14 (4.5)	1	-
Pakka (made by bricks and cement)	942 (97.8)	298 (95.5)	2.11	(1.10- 4.21)
Mother's history of illness				
No	959 (99.6)	305 (97.8)	1	-
Yes	4 (0.4)	7 (2.2)	5.50	(1.60- 18.92)
Family history of illness				
No	556 (57.7)	191(61.2)	1	-
Yes	407 (42.3)	121(38.8)	0.86	(0.72-1.10)
Years of marriage Mean(S.D)	6.1 (5.5)	4.6 (4.6)	0.90	(0.91- 1.00)
Gravidity Mean(S.D)	3.1 (0.1)	2.4 (0.1)	0.82	(0.80-0.91)
History of miscarriage				
No	565 (74.0)	110 (64.0)	1	-
Yes	198 (26.0)	62 (36.0)	1.61	(1.13-2.31)
History of preterm delivery				
No	752 (98.6)	158 (91.9)	1	-
Yes	11(1.4)	14 (8.1)	6.00	(2.71-13.60)
History of still birth				
No	718 (94.1)	142 (82.6)	1	-
Yes	45 (5.9)	30 (17.4)	3.34	(2.13-5.52)
Complication during previous pregnancy				
No	855 (88.8)	261 (83.7)	1	-
Yes	108 (11.2)	51 (16.3)	1.52	(1.10-2.21)

Table 3. Continued.

Booked in the hospital				
Yes	732 (76.0)	204 (65.4)	1	
No	231 (24.0)	108 (34.6)	1.70	(1.32-2.20)
Gestational age when fetal movement started (Weeks)				
Mean(S.E)	20.7 (0.1)	20.7 (0.1)	0.99	(0.94 -1.11)
No. of antenatal care visits	6.5 (0.1)	6.6 (0.2)	1.02	(0.99-1.04)
Micturition problem during pregnancy				
No	793 (82.3)	229 (73.4)	1	
Yes	170 (17.7)	83 (26.6)	1.71	(1.33-2.30)
Taken folic acid tablets				
No	611 (63.4)	199 (63.8)	1	
Yes	352 (36.6)	113 (36.2)	1.02	(0.81-1.30)
Complication during current pregnancy				
No	765 (79.4)	192 (61.5)	1	
Yes	198 (20.6)	120 (38.5)	2.40	(1.80-3.22)
Blood transfusion done				
No	914 (94.9)	286 (91.7)	1	
Yes	49 (5.1)	26 (8.3)	1.70	(1.0-2.80)
Duration between water break and delivery of baby (Hours)				
Mean(S.E)	12.3 (0.7)	27.8 (4.6)	1.03	(1.02-1.03)
Slits/window in the kitchen				
Yes	909 (94.4)	283 (90.7)	1	
No	54 (5.6)	29 (9.3)	1.72	(1.11-2.76)
Tobacco use				
No	728 (75.6)	180 (57.7)	1	
Yes	235 (24.4)	132 (42.3)	2.27	(1.73 -2.97)

Table 4. Multivariate analysis of factors associated with adverse birth outcomes & obstetric complications among cases and controls at selected hospitals in Karachi, Pakistan

Characteristics	Adjusted odds ratio	95 % C.I
Tobacco use		
No	1	
Yes	2.24	(1.56-3.23)
Gravidity	0.83	(0.73-0.93)
Age of mother	1.03	(1.0-1.10)
Booked in hospital		
Yes	1	
No	1.87	(1.38-2.74)
History of Preterm births		
No	1	
Yes	6.04	(2.52- 14.48)
History of miscarriage		
No	1	
Yes	1.91	(1.27 – 2.85)
History of still birth		
No	1	
Yes	4.06	(2.36 – 6.97)
Slit/window in kitchen		
Yes	1	
No	1.90	(1.05 – 3.43)
Blood transfusion done		
No	1	
Yes	3.06	(1.68 – 5.57)

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **√ page 1 & 2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **√ page 2 -3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **√ page 5-7**
Objectives	3	State specific objectives, including any prespecified hypotheses **√ page 7**
Methods		
Study design	4	Present key elements of study design early in the paper **√ page 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **√ page 7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **√ page 8-9**
		(*b*) For matched studies, give matching criteria and the number of controls per case **NA**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **√ page 9-10**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **√ page 9-10**
Bias	9	Describe any efforts to address potential sources of bias **√ page 3 & 15**
Study size	10	Explain how the study size was arrived at **√ page 9**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **√ page 11**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **√ page 11**
		(*b*) Describe any methods used to examine subgroups and interactions **√ page 11**
		(*c*) Explain how missing data were addressed NA
		(*d*) If applicable, explain how matching of cases and controls was addressed **NA**
		(*e*) Describe any sensitivity analyses **NA**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **√ page 9 & 12**
		(b) Give reasons for non-participation at each stage *** No reasons**
		(c) Consider use of a flow diagram NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **√ page 12**
		(b) Indicate number of participants with missing data for each variable of interest NA
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure **√ page 12 & page 22- 24**

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **√ page 12-13 & page 25-27**
		(*b*) Report category boundaries when continuous variables were categorized **NA**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **NA**

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **NA**
Discussion		
Key results	18	Summarise key results with reference to study objectives **√ page 16**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **√ page 3& 15**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **√ page 13-16**
Generalisability	21	Discuss the generalisability (external validity) of the study results *** page 15**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **√ page 17**

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.