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Original Article

The effects of maternal smoking exposure during pregnancy on postnatal outcomes: A cross sectional study

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Abstract

Background: The purpose of this article was to evaluate the effect of maternal smoking exposure during pregnancy on postnatal outcomes.
Methods: This prospective study enrolled 278 pregnant women in the third trimester, who were asked to complete a questionnaire which included inquires about the nature and extent of smoking exposure during their pregnancy. In addition to the questionnaire, each study subject provided urine sample for the measurement of cotinine. Using data generated from this inquiry, we analyzed the association between maternal smoking exposure and birth outcomes.
Results: From the 278 enrollees in this study, a minority of subjects (7.2%) smoked, while 40.6% of the study subjects were exposed to environmental tobacco smoke during pregnancy. There was significantly higher birth weight (3205.2 ± 373.1 vs 3089.7 ± 363.0 vs 2959.0 ± 403.7 g, $p = 0.004$), larger chest size (33.1 ± 1.7 cm vs 32.7 ± 1.5 cm vs 32.0 ± 1.7 cm, $p = 0.009$), higher bilirubin on postnatal day 3 (8.9 ± 1.6 vs 8.6 ± 1.5 vs 7.8 ± 1.4 mg/dL, $p = 0.015$), but lower maternal urinary cotinine level (83.7 ± 132.4 vs 153.2 ± 96.0 vs 800.5 ± 1027.8 μg/g creatinine, $p < 0.001$) in smoking-free status than in passive or active smoking status. Significant risks of birth weight < 2500 g (AOR 3.93 (95% CI 1.61–9.59), $p = 0.003$) and maternal urinary cotinine ≥ 143 μg/g creatinine (AOR 3.38 (95% CI 2.02–5.66), $p < 0.001$) were observed as smoking exposure increased. There was significantly higher birth weight ($p = 0.048$), larger chest size ($p = 0.045$), and higher bilirubin level on postnatal day 3 ($p < 0.001$) in the group with cotinine <143 μg/g creatinine than in the group with cotinine ≥ 143 μg/g creatinine.
Conclusion: Our results demonstrated that maternal smoking exposure during pregnancy is associated with low birth weight and small chest circumference. Although the incidence of active smoking in Taiwanese pregnant women is low, most of them are exposed to passive smoking environment. Further studies are required to evaluate useful interventions to enhance a smoking-free environment during pregnancy.
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Keywords: Birth outcome; Cotinine; Pregnant women; Smoking

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

It is well documented that smoking exposure during pregnancy is associated with multiple adverse effects on the fetus. Active maternal smoking increases the risks of perinatal mortality, preterm delivery, miscarriage, ectopic pregnancy, antepartum hemorrhage, placenta previa, placental abruption, fetal growth restriction, low birth weight (LBW) and sudden infant death syndrome.[1–4] However, the effects of passive maternal smoking, also known as environmental tobacco exposure (ETS), have been less well studied and thus have generated less consistency in the literature. It can also cause harmful effects to the fetus, including LBW, fetal death, preterm delivery and spontaneous abortion.[5–7]

In Taiwan, the prevalence of male and female adult smokers in 2010 is 35.0% and 4.1%, respectively.[8] Lin et al. reported the prevalence of smoking in young military conscripts even exceeds 50%.[9,10] There are some Taiwanese studies about the effect of smoking exposure during pregnancy.[8,11–14] Chen et al.'s study suggests that clinicians can target interventions designed to increase pregnant women's self-efficacy, advising women to try to establish their own smoking policy at home.[11] Wang et al. reported that smoke exposure during pregnancy might increase the risk of atopic dermatitis in children.[12] Lai et al. found that most women stop smoking during pregnancy; however, most women continue to be exposed to passive-smoking environments.[13] Ko et al.'s study demonstrated that maternal smoking is responsible for increased incidences of LBW and preterm delivery of babies.[8] Lai et al.'s study showed that understanding the risk factors associated with smoking and exposure to second-hand smoke during pregnancy may help in the development of strategies to reduce such exposure.[14] Most of the previous researches only measured smoke exposure by patient survey recall, which may be more likely to be subject to misclassification of exposure.[15] Cotinine is a major metabolite of nicotine with a longer half-life and thus a more accurate measure of total exposure than questionnaire methods.[16,17]

The purpose of this prospective study was to evaluate the effect of smoking exposure on the fetus by both questionnaire assessment and urinary cotinine measurement in southern Taiwan.

2. Methods

2.1. Subjects

This prospective study was conducted from March 2009 to February 2010 at the department of Obstetrics and Gynecology at Fooyin University Hospital. Three hundred pregnant women during their third-trimester prenatal checkups (after 24 weeks) were screened for study. Eighteen subjects were excluded because of chronic diseases (diabetes mellitus, hypertension), infectious diseases, twins, and stillbirth leaving 282 eligible candidates. Four of these women did not want to participate in the study, leaving 278 subjects, all of whom signed written consent forms. The final enrolled subjects thereafter each completed questionnaires, which inquired about the nature and extent of their smoking, and their smoking exposure during pregnancy. Each subject provided a urine sample for the measurement of cotinine, and the medical records of all neonates were reviewed. More specifically, the medical records were reviewed for age, sex, birth weight, body length, head and chest circumference, and bilirubin level. They were divided into three groups: active smoking status (smoking or smoking & ETS), passive smoking status (non-smoking & ETS), and smoking-free status (non-smoking & non-ETS).

2.2. Research ethics

This study was approved by the Institutional Review Board of Fooyin University Hospital (FYH-IRB-97006). Written informed consents were obtained from all adult women and from guardians on behalf of subjects less than 20 years of age who were involved in this study.

2.3. Questionnaire

A questionnaire was modified from similar templates in the previous literatures on smoking during pregnancy.[5–7] Content validity of the questionnaire was assessed by an expert panel consisting of 6 experts in nursing, health education, and smoking cessation. After gathering opinions from the experts, those questions without precise contents were excluded. Thereafter, well-trained interviewers administered the questionnaires, collecting demographic and smoking habits and self-reported ETS exposure at different locations during pregnancy. The questionnaire consisted of several sections, including demographics, health status, household smoking habits and self-reported ETS exposure at different locations, alcohol drinking, areca use, etc. Demographic questions included age, body weight, body length, ethnicity, marital status, education level, employment status, and last menstrual period. The questions about smoke exposure included: (1) Do you smoke during pregnancy? (2) Does your husband smoke? (3) Do your family smoke? (4) Are you exposed to other ETS in home or workplace etc. The definition of “smoking” exposure for the purpose of this study was derived from the subject's responses to the above-mentioned smoking questionnaire. During the period of pregnancy, three groups of smoking exposure were created, namely: (1) “active smoking” (reported being a smoker during pregnancy with/without ETS), (2) “passive smoking” (reported being a non-smoker during pregnancy with ETS at home or workplace), and (3) “smoking-free” (reported being a non-smoker during pregnancy without ETS), respectively.

2.4. Urine cotinine measurement

The urine samples of the participating subjects were collected, centrifuged, and the supernatant was stored at −30 °C until it was analyzed within 6 months. The enzyme immunoassay (EIA) kit for cortinine was (DRI® Cotinine,

Microgenics Corp., Fremont, CA, USA) and measured by an automatic analyzer (HITACHI; model 7180, South Korea). The assay is based on competition between continine labeled with glucose-6-phosphate dehydrogenase (G6PDH) enzyme and free cotinine in the sample for a fixed amount of cotinine-specific antibody binding sites. The enzyme G6PDH activity is determined spectrophotometrically at 340 nm by measuring its ability to convert nicotinamide adenine dinucleotide (NAD) to NADH. All assay procedures followed the EIA kit manufacturers. The urinary creatinine was also analyzed simultaneously by using the same analyzer. The data is shown as cotinine μg/g creatinine (cre).

2.5. Statistical analysis

Data are expressed as mean ± standard deviation or numbers with percentages. Categorical data were analyzed using chi-squared analyses, and continuous variables were computed using independent Student's *t*-tests. A receiver operating characteristics (ROC) curve was generated and the area under the curve (AUC) was calculated to evaluate the specificity and sensitivity for dichotomization of maternal urinary cotinine level. The one way ANOVA and Scheffe's test were set up to examine the differences of birth body weight, body length, head circumference, chest circumference, and newborn bilirubin levels in the 3 maternal groups with/without smoking and ETS. The Kruskal−Wallis one way ANOVA and the Mann−Whitney *U* test were used to examine the difference of maternal urinary cotinine levels in the 3 maternal groups with/without smoking and ETS. A linear trend test was used to evaluate the dose effect of increased smoking on birth body weight and cotinine level. Unadjusted odds ratios and fully adjusted odds ratios were reported after logistic regression analysis. The significance of p value was set at 0.05. All analysis was performed using SPSS software (version 20, SPSS Institute Inc., Chicago, IL, USA) and SAS (version 9.3, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of subjects

The 278 enrolled subjects had a mean age 27.6 ± 4.5 years, and thirty one (11.2%) of the participants were foreign. Demographic and clinical data of subjects were shown in Table 1. Furthermore, the percentage of subjects with an education level of high school or below was 72.3%, a minority of subjects (7.2%) smoked during pregnancy, and 40.6% of subjects were exposed to environmental tobacco smoke during pregnancy. Out of all 278 women in this study, 59% of their husbands smoked, few subjects (18.3%) had parity ≥3, most subjects (71.9%) had full-term delivery, and most subjects (75.9%) were healthy (18.5 ≤ BMI < 25). There was 4.7% of neonates with birth weight <2500 g. The mean birth weight, height, head size, and chest size were 3140.5 ± 377.4 (g), 50.0 ± 2.2 (cm), 34.4 ± 1.4 (cm), and 32.8 ± 1.6 (cm) respectively.

3.2. The relationship of birth outcomes, newborn bilirubin, maternal cotinine with maternal smoking exposure status

Table 2 showed the data about birth outcomes, newborn bilirubin and maternal urinary cotinine level in the different maternal smoking statuses. There was significantly higher birth weight (3205.2 ± 373.1 vs 3089.7 ± 363.0 vs 2959.0 ± 403.7 g, $p = 0.004$), larger chest size (33.1 ± 1.7 vs 32.7 ± 1.5 vs 32.0 ± 1.7 cm, $p = 0.009$), and higher bilirubin on postnatal day 3 (8.9 ± 1.6 vs 8.6 ± 1.5 vs 7.8 ± 1.4 mg/dL, $p = 0.015$), in the smoking-free status than in the passive smoking or active smoking status. In addition, there was significant higher maternal urinary cotinine level in the active smoking status than in the passive smoking or smoking-free status (800.5 ± 1027.8 vs 153.2 ± 96.0 vs 83.7 ± 132.4 μg/g cre, $p < 0.001$). However, there was no significant difference in the three smoking exposure groups in terms of height and head size. Compared to that risk in the smoking-free status, the risk of birth weight < 2500 g was significantly higher in the active smoking status (AOR 15.88 (95% CI: 2.49−101.34), $p = 0.003$) (Table 3). A significant linear trend of risk of birth weight < 2500 g was observed as the smoking exposure increased (AOR 3.93 (95% CI 1.61−9.59), $p = 0.003$) (Table 3). For logistic regression analysis, subjects were divided into two groups with maternal urinary cotinine level≥ or <143 μg/g cre based on the ROC curve analysis in Fig. 1 (sensitivity 77.8%, specificity 86.5%, AUC = 0.823, $p < 0.001$). Compared to that risk in the smoking-free status, the risk of maternal urinary cotinine ≥ 143 μg/g cre was significantly higher in the active smoking status (AOR 27.30 (95% CI: 7.91−94.28), $p < 0.001$) (Table 4). A significant linear trend of risk of maternal urine cotinine ≥ 143 μg/g cre was observed as the smoking exposure increased (AOR 3.38 (95% CI 2.02−5.66), $p < 0.001$) (Table 4).

3.3. Comparison of birth outcomes and newborn bilirubin between two groups with maternal urinary cotinine level≥ or <143 μg/g cre

There was significantly higher birth weight (3148.4 ± 368.4 vs 3106.4 ± 416.4 g, $p = 0.048$), and larger chest size (32.9 ± 1.6 vs 32.2 ± 1.8 cm, $p = 0.045$) in the group with cotinine <143 μg/g cre than in the group with cotinine ≥ 143 μg/g cre. Comparison of birth outcomes and newborn bilirubin between two groups with maternal urinary cotinine level≥ or <143 μg/g cre was presented in Table 5. There was also significantly higher bilirubin level on postnatal day 3 (9.31 ± 1.43 vs 7.76 ± 1.23 mg/dL, $p < 0.001$) in the group with cotinine <143 μg/g cre than in the group with cotinine ≥ 143 μg/g cre. There was no significant difference between the two groups in terms of height and head size.

4. Discussion

Our results demonstrated that maternal smoking exposure is associated with LBW, small chest circumference and low

Table 1
The demographic and clinical data of subjects (N = 278 pairs).

Characteristics	Mothers	Characteristics	New born
	N (%)		N (%)
Ethnicity		Gender	
Taiwanese	217 (78.1)	Male	148 (53.2)
Hakka	14 (5.0)	Female	130 (46.8)
Aborigine	16 (5.8)	Birth weight(g)	3140.5 ± 377.4
Foreign	31 (11.2)	<2500 g	13 (4.7)
Age (year)	27.6 ± 4.5	≥2500 g	265 (95.3)
<20	4 (1.4)	Height (cm)	50.0 ± 2.2
20–35	263 (94.6)	Head size (cm)	34.4 ± 1.4
>35	11 (4.0)	Chest size (cm)	32.8 ± 1.6
Employment during pregnancy			
No	148 (53.2)		
Yes	130 (46.8)		
Education			
High school and below	201 (72.3)		
University and above	77 (27.7)		
Maternal smoking status (urinary cotinine (μg/g creatinine))			
Smoking-free (83.7 ± 132.4)	145 (52.2)		
Passive smoking (153.2 ± 96.0)	113 (40.6)		
Active smoking (800.5 ± 1027.8)	20 (7.2)		
Paternal smoking			
No	114 (41.0)		
Yes	164 (59.0)		
Areca chewing while pregnancy			
No	273 (98.2)		
Yes	5 (1.8)		
Parity			
1st	111 (39.9)		
2nd	116 (41.7)		
3rd and above	51 (18.3)		
Gestational weeks at birth			
Pre-term (<37 weeks)	78 (28.1)		
Full term (≥37 weeks)	200 (71.9)		
Pre-pregnancy BMI (kg/m^2)			
Underweight (BMI < 18.5)	29 (10.4)		
Healthy (18.5 ≤ BMI < 25)	211 (75.9)		
Overweight (25 ≤ BMI < 30)	29 (10.4)		
Obese (BMI ≥ 30)	9 (3.2)		

Table 3
Risk of birth weight < 2500 g in different maternal smoking exposure status.

Maternal smoking status	Birth weight (<2500 g vs ≧2500 g)			
	OR (95% CI)	*p*	AOR (95% CI)	*p*[a]
Smoking-free	1.00		1.00	
Passive smoking	4.72 (0.96–23.19)	0.056	4.53 (0.91–22.46)	0.065
Active smoking	17.88 (3.03–105.39)	0.001	15.88 (2.49–101.34)	0.003
Test for trend	4.17 (1.78–9.77)	0.001	3.93 (1.61–9.59)	0.003

[a] Values have been adjusted for maternal age, maternal BMI, and gestational weeks at birth. AOR = adjusted odds ratio; OR = odds ratio.

newborn bilirubin. These findings are consistent with the previous reports about the effects of smoking exposure on the fetus.[1–8,18–21] Our study further elucidates the effect of maternal smoking exposure, including ETS, on perinatal outcomes.

In this study, the incidence of active smoking in pregnant women was only 7.2%, while 40.6% of the subjects were exposed to ETS. A Taiwanese study by Lai et al.[13] showed the incidence of active smoking in pregnant woman is 5.6% in 2013. The incidence of active smoking in pregnant women appears to decrease gradually in Taiwan, but most of the women continue to be exposed to passive-smoking environments.[13] Our result is in agreement with their finding.[13] The incidence of active smoking among pregnant women is variable around the world, reaching the level of about 3.8–10.0% in Japan,[22] 10.7% in the United States,[23] 18% in Spain,[24] 19.9% in Poland,[25] and 22.9% in Portugal.[26] The prevention of smoking exposure during pregnancy is still an important global issue and requires further research. Both pregnant women and their close family should be educated about the potential harms of active and passive smoking to the pregnant women and their babies. Only smoke-free environments can prevent the risks of smoking exposure.

Both maternal smoking exposure and cotinine level are associated with low birth weight in this series. Nicotine/cotinine can cross the placenta barrier and affect the fetal growth, resulting in the subsequent loss of weight in babies at birth.[27] Gupta et al. showed that consumption of smokeless tobacco during pregnancy decreases gestational age at birth and birth weight independent of gestational age.[6] Kharrazi et al. reported that ETS exposure in pregnant women adversely affects pregnancy by increasing fetal mortality and preterm delivery

Table 2
Birth outcomes, newborn bilirubin and maternal urinary cotinine level in different smoking status (278 pairs).

Variable	Smoking-free		Passive smoking		Active smoking		*p*
	N (%)	Mean ± SD	N (%)	Mean ± SD	N (%)	Mean ± SD	
Weight (g)	145 (52.2)	3205.2 ± 373.1[ab]	113 (40.6)	3089.7 ± 363.0[a]	20 (7.2)	2959.0 ± 403.7[b]	0.004*
Height (cm)	145 (52.2)	50.2 ± 2.1	113 (40.6)	49.9 ± 2.1	20 (7.2)	49.3 ± 2.6	0.151*
Head size (cm)	145 (52.2)	34.5 ± 1.4	113 (40.6)	34.3 ± 1.3	20 (7.2)	34.1 ± 1.4	0.170*
Chest size (cm)	145 (52.2)	33.1 ± 1.7[c]	113 (40.6)	32.7 ± 1.5	20 (7.2)	32.0 ± 1.7[c]	0.009*
Newborn bilirubin (mg/dL)[a]	43 (42.16)	8.9 ± 1.6[de]	49 (48.04)	8.6 ± 1.5[df]	10 (9.8)	7.8 ± 1.4[ef]	0.015*
Maternal cotinine (μg/g creatinine)	145 (52.2)	83.7 ± 132.4[gh]	113 (40.6)	153.2 ± 96.0[gi]	20 (7.2)	800.5 ± 1027.8[hi]	<0.001†

*p-values was estimated by one-way ANOVA test.
†p-values was estimated by Kruskal–Wallis one-way ANOVA test.
[a]$P = 0.048$; [b]$P = 0.022$; [c]$P = 0.024$; [d]$P = 0.046$; [d]$P = 0.012$; [f]$P = 0.018$; [g]$P = 0.015$; [h]$P < 0.001$; [i]$P < 0.001$.
[a] Means bilirubin level on day3.

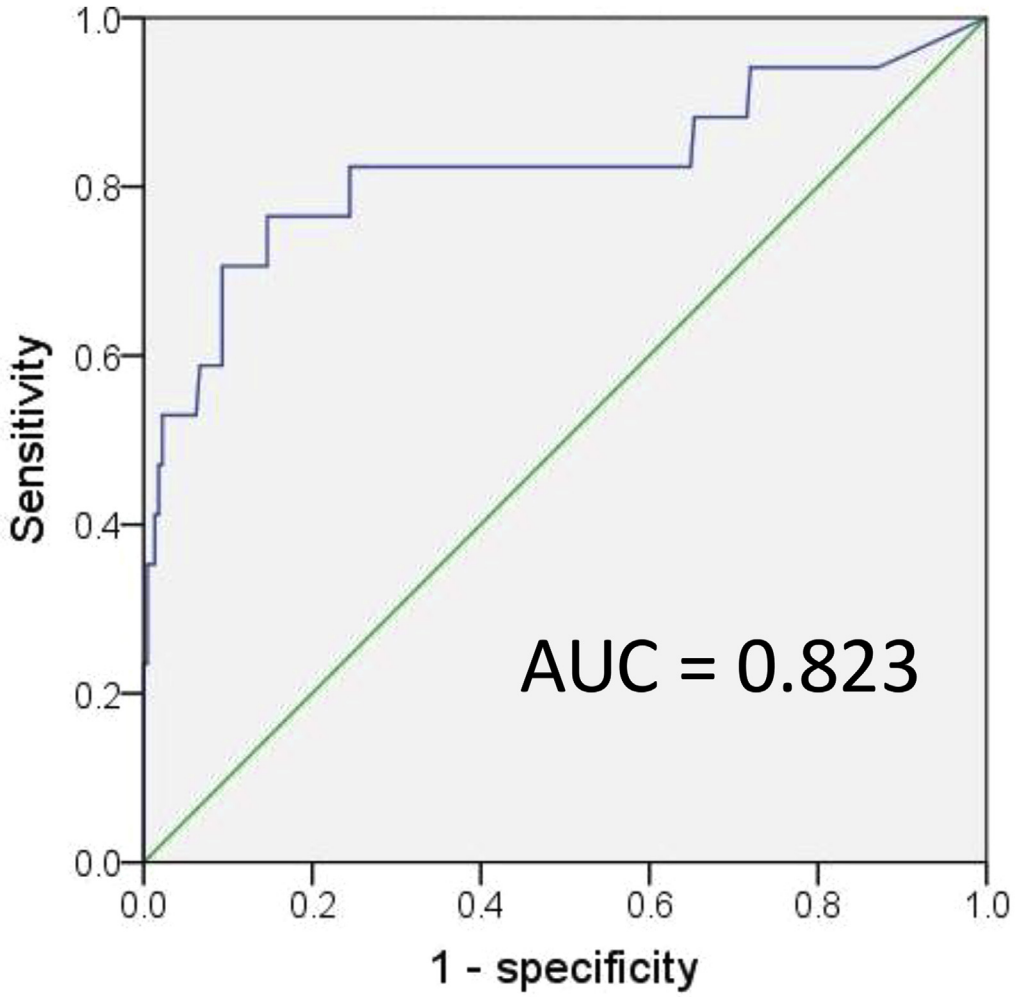

Fig. 1. The receiver operating characteristic curve analysis for dichotomization of maternal urinary cotinine level with a cut-off value of 143 μg/g creatinine. AUC: area under the curve.

at higher exposure levels and slowing fetal growth across all levels of ETS exposure.[7] Gray et al. demonstrated that reduced birth weight, gestational age, or head circumference were observed if meconium contained one or more tobacco biomarkers.[28] Lindley et al. reported smoking during pregnancy was associated with reductions in birth weight, and the harmful effects were worse with heavier smoking.[29] They further found quitting smoking sometime between the first prenatal care visit and GA 32 weeks lead to complete elimination of the smoking-associated low birth weight.[29] Ko et al.'s study demonstrated that maternal smoking is responsible for the increased incidences of LBW and preterm delivery of babies in Taiwan.[8] These previous literatures are compatible with our finding. Further research including smoking cessation interventions will help pregnant women avoid the harmful effects of smoking.

Table 4
Risk of urinary cotinine level ≥ 143 μg/g in different maternal smoking exposure status.

Maternal smoking status	Cotinine (≥143 vs <143 μg/g)			
	OR (95% CI)	*p*	AOR (95% CI)	*p*[a]
Smoking-free	1.00		1.00	
Passive smoking	1.34 (0.66−2.71)	0.420	1.32 (0.65−2.70)	0.446
Active smoking	28.22 (8.49−93.86)	<0.001	27.30 (7.91−94.28)	<0.001
Test for trend	3.48 (2.11−5.73)	<0.001	3.38 (2.02−5.66)	<0.001

[a] Values have been adjusted for maternal age. Maternal urinary cotinine was corrected by creatinine (μg/g). AOR = adjusted odds ratio; OR = odds ratio.

The current data revealed that low chest circumference is significantly associated with maternal smoking exposure. There is limited data about the effect of smoking exposure on neonatal chest circumference. Polańska et al. reported that polycyclic aromatic hydrocarbon (an important source of tobacco smoke) was negatively associated with chest circumference.[18] Nicotine exposure via maternal tobacco smoking can affect critical stages of lung development and can permanently alter lung structure and hence lung function.[30] In utero tobacco exposure is responsible for an increase in alveolar volumes and a decrease in the caliber of airway walls.[31] The animal study by Sekhon et al.[32] showed that pregnant monkeys exposed to nicotine gave birth to their offspring with alveolar hypoplasia. Other animal studies have had similar findings with impaired lung growth and alveolar

Table 5
Comparison of birth outcome between different maternal urinary cotinine groups.

	Cotinine < 143 μg/g creatinine		Cotinine ≥ 143 μg/g creatinine		*p*
	N	mean ± SD	N	mean ± SD	
Weight (g)	226	3148.4 ± 368.4	52	3106.4 ± 416.4	0.048
Height (cm)	226	50.0 ± 2.1	52	49.9 ± 2.5	0.805
Head size (cm)	226	34.4 ± 1.4	52	34.6 ± 1.3	0.388
Chest size (cm)	226	32.9 ± 1.6	52	32.2 ± 1.8	0.045
Bilirubin (mg/dL)[a]	68	9.31 ± 1.43	34	7.76 ± 1.23	<0.001

[a] Means bilirubin level on day 3 of age.

development.[33,34] Both clinical and animal studies demonstrated the harmful effects of maternal smoke exposure on fetal lung, resulting in lung hypoplasia. Their results may partially explain the negative association of maternal smoke exposure and chest circumference in this series. Further studies are required to explain the structural and functional disturbances of lung related to maternal smoke exposure.

We observed the significant association of high maternal urinary cotinine with low newborn bilirubin on postnatal day 3. Hardy et al. first reported that maternal cigarette-smoking significantly depressed fetal serum bilirubin levels.[19] Nymand confirmed Hardy et al.'s finding[19] and speculated that cyanide originating from tobacco smoke enters the fetal circulation and is detoxified in the fetal liver, which results in the induction of glucuronyl-transferase and enhances the excretion of conjugated bilirubin from the liver, resembling a mechanism known from the action of phenobarbitone on neonatal serum bilirubin levels.[35] The findings of Divian et al. showed that infants whose mother smoked cigarettes during pregnancy were at lower risk of neonatal jaundice relative to infants of nonsmokers.[20] Knudsen's study suggested that maternal smoking may affect the postnatal plasma bilirubin concentration in offspring by various mechanisms.[21] These previous studies[19–21,35] and ours showed low newborn bilirubin in maternal smoking exposure. On the contrary, Hoff et al. reported that neonates born to women smoking more than or equal to one-half pack per day had a higher frequency of jaundice.[36] The relationship between smoking exposure and newborn bilirubin level remains controversial. However, further studies are needed to elucidate the role of maternal smoking exposure on bilirubin metabolism.

There are several limitations in this cross-sectional study. This is a single-center investigation with limited number of patients. Questionnaires and urine collection were done only in the third trimester. The components of smoking exposure except cotinine were not measured. The potential effect of smoking on drugs[37] and risk of prenatal infection[38] during pregnancy were not evaluated. Newborn bilirubin data were not complete. Longitudinal studies with large cohorts and detailed data are required to evaluate the effect of maternal smoking exposure on fetus.

In conclusion, maternal smoking exposure is associated with LBW, small chest circumference and low newborn bilirubin in this series. The incidence of active smoking in Taiwanese pregnant women is low, but most of them are exposed to passive smoking environment. Further studies are required to evaluate the effectiveness of potentially useful interventions in enhancing smoking-free environment during pregnancy.

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