Association between Serum Cotinine Levels, Fetal Biometry, and Umbilical Artery Flow in Pregnant Women Exposed to Secondhand Smoke

Margaret Diana, Deviana Soraya Riu, Fatmawati Madya, St. Maisuri T. Chalid, Nasrudin AM, Telly Tessy

Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Hasanuddin, Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia

Correspondence: Margaret Diana, Email: margaretdiana@gmail.com

Abstract

Objective: This study aimed to investigate the impact of SHS exposure on fetal biometry and umbilical artery flow at 24 – 28 weeks of gestation.

Methods: This cross-sectional study included 110 pregnant women, divided into a study group (55 passive) smokers and a control group (55 non-passive smokers). Serum cotinine levels were measured using ELISA. Fetal biometry (biparietal diameter, head circumference, abdominal circumference, and femur length) and umbilical artery flow (pulsatility and resistance indices) were assessed via ultrasound and Doppler ultrasonography. Group comparisons were conducted using Chi-square and independent t-tests.

Results: The passive smoker group had significantly higher mean serum cotinine levels compared with the control group (10.97 ng/mL vs. 4.53 ng/mL; $p = 0.01$). However, no statistically significant differences ($p > 0.05$) were found in any of the fetal biometric parameters or umbilical artery flow indices between the groups. Correlation analyses also showed no significant association between cotinine levels and the measured fetal outcomes.

Conclusion: In this second-trimester study, SHS exposure, confirmed by elevated cotinine levels, was not associated with measurable adverse effects on fetal biometry or umbilical artery flow. These non-significant findings underscore the need for longitudinal research to evaluate the cumulative impact of SHS, particularly in the third trimester and on final birth outcomes.

Keywords: Secondhand smoke exposure; cotinine; fetal biometry; umbilical artery flow

Hubungan antara Kadar Kotinin Serum, Biometri Janin, dan Aliran Arteri Umbilikalis pada Ibu Hamil yang Terpapar Asap Rokok Pasif

Abstrak

Tujuan: Penelitian ini bertujuan untuk menelaah dampak paparan asap rokok pasif terhadap biometri janin dan aliran arteri umbilikalis pada usia kehamilan 24 – 28 minggu.

Metode: Penelitian potong lintang ini melibatkan 110 ibu hamil yang dibagi menjadi kelompok studi (55 perokok pasif) dan kelompok kontrol (55 bukan perokok pasif). Kadar kotinin serum diukur menggunakan metode ELISA. Biometri janin (meliputi diameter biparietal, lingkar kepala, lingkar perut, dan panjang femur) serta aliran arteri umbilikalis (indeks pulsasi dan indeks resistensi) dinilai melalui ultrasonografi (USG) dan USG Doppler. Perbandingan antarkelompok dianalisis menggunakan uji Chi-square dan uji t independen.

Hasil: Kelompok perokok pasif memiliki rerata kadar kotinin serum yang secara signifikan lebih tinggi dibandingkan kelompok kontrol (10,97 ng/mL vs. 4,53 ng/mL; $p = 0,01$). Namun, tidak ditemukan perbedaan bermakna secara statistik ($p > 0,05$) pada parameter biometri janin maupun indeks aliran arteri umbilikalis antara kedua kelompok. Analisis korelasi juga tidak menunjukkan adanya hubungan bermakna antara kadar kotinin dengan luaran janin yang diukur.

Kesimpulan: Pada penelitian trimester kedua ini, paparan asap rokok pasif yang dikonfirmasi dengan peningkatan kadar kotinin tidak berhubungan dengan efek merugikan yang terdeteksi pada biometri janin maupun aliran arteri umbilikalis. Temuan yang tidak signifikan ini menekankan pentingnya penelitian longitudinal untuk menilai dampak kumulatif paparan asap rokok pasif, terutama pada trimester ketiga dan luaran kelahiran akhir.

Kata kunci: Aliran arteri umbilikalis; biometri janin; kotinin; paparan asap rokok pasif

 DOI: 10.24198/obgynia.v8i3.956

Introduction

Cigarette smoke contains more than 4,000 chemical compounds, over 200 of which are toxic. Exposure to tobacco smoke is particularly harmful to vulnerable populations, including pregnant women, who are frequently exposed to secondhand smoke (SHS) from partners or colleagues.[1] Both active and passive smoking during pregnancy increase the risk of complications such as spontaneous abortion, premature birth, stillbirth, placenta previa, and placental abruption.[2] Furthermore, maternal exposure to tobacco smoke is a major risk factor for sudden infant death syndrome (SIDS), contributing to nearly 25% of all cases.[3] Infants exposed in utero are also at increased risk of low birth weight, impaired brain development, cleft lip and palate, and other growth disorders.[3,4]

Previous research indicates that SHS exposure during pregnancy may adversely affect fetal biometry and placental vascular resistance. Even minimal exposure can disrupt fetomaternal circulation. It is hypothesized that substances in tobacco smoke, including nicotine and carbon monoxide, impair umbilical artery flow by increasing placental vascular resistance.[5]

Cotinine, the primary metabolite of nicotine, is a reliable biomarker of tobacco smoke exposure and can be measured in serum, urine, hair, or saliva. While many studies have correlated cotinine levels with SHS exposure, few have directly examined their effect on specific fetal outcomes.[4,5] Therefore, this study aimed to investigate the impact of SHS exposure at 24 – 28 weeks of gestation on fetal biometry and umbilical artery flow.

Methods

This cross-sectional study was conducted from November 2016 to January 2017 at several hospitals affiliated with the Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Hasanuddin. The study population consisted of women at 24 – 28 weeks of gestation attending antenatal care (ANC) clinics. The study group included pregnant women identified as passive smokers, while the control group comprised pregnant women with no exposure to tobacco smoke. Exclusion criteria for both groups were: active smoking during pregnancy, complicated pregnancies (such as preeclampsia or gestational diabetes), and any other maternal diagnosis unrelated to tobacco exposure that could potentially result in a diagnosis of small for gestational age.

Data collection followed several procedures. Participants were recruited using purposive sampling. A total of 110 women were enrolled and allocated into two groups of 55, with recruitment continuing until the target sample size for each group was achieved. Serum cotinine levels were measured using an enzyme-linked immunosorbent assay (ELISA). Fetal biometry was assessed via abdominal ultrasound, which included measurements of biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). Concurrently, Doppler ultrasonography was used to evaluate umbilical artery blood flow, measured by the pulsatility index (PI) and resistance index (RI).

Statistical analyses were conducted to compare the two groups. Differences in categorical variables were analyzed using the Chi-square test, while continuous variables were compared using the independent t-test. A p-value of less than 0.05 was considered statistically significant. Multivariate analyses were planned to evaluate the combined impact of significant variables on abnormal fetal biometry, to be performed only if multiple predictors were identified in the initial analyses.

The study received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin, Makassar (530/H04.8.4.5.31/PP36-KOMETIK 2016). Written informed consent was obtained from all participants before enrollment.

Results

The study enrolled a total of 110 pregnant women, who were allocated into a study group (n = 55) and a control group (n = 55). An analysis of baseline characteristics revealed no statistically significant differences between the two groups in terms of age, parity, or education level (p > 0.05 for all). For example, the proportion of multiparous women was slightly higher in the study group (56.4%) compared to the control group (49.1%), but this difference was not significant. The complete demographic data are presented in Table 1. Given that no significant baseline differences were identified, these variables were not considered potential confounders; therefore, a multivariate analysis was not conducted.

Table 1 Characteristics of Pregnant Women

Characteristics (n %)	Study group (n = 55)	Control (n = 55)	*P*	OR (95% CI)
Age (years)				
<20 and >30	29 (52.7)	33 (60)	0.564	0.75 (0.34 - 1.62)
20-35	26 (47.3)	22 (40)		
Parity				
Nulliparous/primiparous	24 (43.6)	28 (50.9)	0.567	0.74 (0.34 - 1.62)
Multiparous	31 (56.4)	27 (49.1)		
Education (years)				
<9	16 (29.1)	15 (27.3)	0.65	1.09 (0.49 - 2.46)
≥9	39 (70.9)	40 (72.8)		

Table 2 Cotinine Levels, Fetal Biometry, and Umbilical Arterial Blood Flow

Measurement	Study group (mean ± SD)	Control (mean ± SD)	*p*
Fetal biometry (mm)			
BPD	59.00 ± 7.51	61.64 ± 7.51	0.068
FL	44.95 ± 6.46	44.09 ± 6.52	0.492
HC	219.38 ± 27.06	224.85 ± 26.39	0.285
AC	188.96 ± 23.99	197.78 ± 27.10	0.074
Umbilical arterial flow			
PI	1.25 ± 0.15	1.26 ± 0.16	0.718
RI	0.752 ± 0.03	0.750 ± 0.03	0.767
Cotinine levels (ng/ml)	10.97	4.53	0.01

Legend: biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), pulsatility index (PI), resistance index (RI).

Table 3 Correlation Between Cotinine Levels, Fetal Biometry, and Umbilical Arterial Blood Flow

Fetal biometry	Cotinine levels		PI		RI	
	r	p	r	p	r	p
BPD	-0.057	0.553	-0.08	0.404	-0.07	0.496
FL	-0.015	0.88	-0.022	0.822	0.062	0.52
HC	-0.01	0.919	-0.049	0.614	-0.011	0.91
AC	-0.141	0.143	-0.165	0.082	-0.2	0.036
PI	0.092	0.34		-		-
RI	0.052	0.587		-		-

Legend: biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), pulsatility index (PI), resistance index (RI).

The primary biochemical analysis showed that mean serum cotinine levels were significantly higher in the study group (10.97 ng/mL) compared to the control group (4.53 ng/mL; $p = 0.01$). However, no significant differences ($p > 0.05$) were found between the groups in mean values for fetal biometry, including BPD, FL, HC, and AC (Table 2).

Further correlational analysis indicated a weak, non-significant negative correlation between cotinine levels and fetal biometric measurements. Similarly, a very weak and non-significant positive correlation was observed between cotinine levels and umbilical artery blood flow indices (Table 3).

Discussion

The placenta is a vital organ that performs respiratory, metabolic, and nutritional functions for the fetus.[6] Any placental impairment can therefore have a direct impact. Toxic metabolites from tobacco smoke, such as carbon monoxide (CO) and cotinine, can cross the placental barrier.[5] Cotinine, a potent vasoconstrictor, can reduce placental perfusion and lead to hypoxia. This hypoxic state may trigger endothelial dysfunction, marked by an increase in inflammatory molecules such as nitric oxide and tumor necrosis factor-α.[7] Both cotinine and CO can also induce premature placental aging, impairing its overall function and contributing to low birth weight.[8] The significantly higher cotinine levels found in our study group confirm their exposure to tobacco smoke, making these pathological mechanisms a relevant concern.

Our study found no significant differences in fetal biometry between the passive smoker group and the control group. This aligns with findings from Eskenazi et al., who also reported a non-significant correlation between second-trimester cotinine levels and fetal biometric measurements.[9] However, other studies have shown contrasting results. For instance, Wadi reported that women exposed to secondhand smoke from more than five cigarettes per day had decreased birth weight.[10]

The discrepancy between our results and those of other studies may be explained by the timing of assessment. We performed a single examination during the second trimester, a period when fetal growth is less pronounced compared to the third trimester, when weight gain accelerates significantly.[11] The adverse effects of smoke exposure on growth may therefore only become measurable later in pregnancy. Furthermore, fetal growth is influenced by numerous factors not controlled for in this study, such as maternal genetics, nutrition, and BMI.[12]

Consistent with the biometry results, we found no significant correlation between cotinine levels and umbilical artery flow. This is supported by Newnham et al., who also reported no significant differences in second-trimester umbilical artery Doppler values between women exposed to secondhand smoke and unexposed controls.[12] It is well established that umbilical artery flow can be affected by other variables such as maternal age, ethnicity, and parity.[13] Additionally, studies by Parra-Saavedra et al. suggest that perfusion changes, particularly in the uterine artery, become more evident in the third trimester. This indicates that Doppler assessments for detecting growth-related issues may be more effective later in pregnancy, which could explain the lack of significant findings in our second-trimester measurements.[14]

While our study did not find a significant correlation, other research demonstrates clearer impacts. Yildirim et al. reported that both active and passive smoking dramatically increase blood flow resistance in the uterine and umbilical arteries. This increased resistance can negatively affect the fetus, leading to complications such as intrauterine growth restriction (IUGR), lower birth weight, and preterm birth. Their findings showed that Doppler indices for pulsatility and resistance were noticeably higher in passive smokers compared to non-smokers. This evidence suggests that even passive smoke exposure can cause quantifiable physiological changes in placental circulation, underscoring a potential risk that our second-trimester, cross-sectional design may not have been able to detect.[15]

This study has several limitations that must be considered when interpreting the results. The primary limitation is the cross-sectional design, which captures data at a single point in time (24 – 28 weeks' gestation) and cannot establish causality. The non-significant findings for fetal biometry and umbilical artery flow may be due to this timing, as the most critical period for fetal weight gain occurs in the third trimester.

Furthermore, the use of purposive sampling may have introduced selection bias, potentially limiting the generalizability of our findings. The initial classification of participants relied on self-reported exposure, which is subject to recall bias. Although serum cotinine was used for biochemical confirmation, numerous confounding variables known to affect fetal growth (such as maternal nutrition, BMI, and genetics) were not controlled for. Due to these limitations, the non-significant results of this study do not rule out a harmful effect of secondhand smoke and have limited immediate clinical implications for changing antenatal screening protocols.

To overcome these limitations, future research should employ a longitudinal cohort design. This approach would follow participants from early pregnancy through delivery, allowing for multiple measurements of fetal biometry and Doppler indices, especially during the critical third trimester. Such a design would also enable the collection of more definitive outcomes at birth, such as birth weight, gestational age, and Apgar scores. To enhance validity, future studies should use random sampling from larger, more diverse populations and collect detailed data on potential confounders such as maternal nutrition and BMI. This comprehensive data would permit robust multivariate analyses to better isolate the specific effects of secondhand smoke exposure.

Conclusion

While secondhand smoke exposure was confirmed by significantly higher cotinine levels, this study did not detect an adverse effect on fetal biometry or umbilical artery flow at 24 – 28 weeks' gestation. Future longitudinal studies are essential to fully understand the impact of secondhand smoke, particularly in the third trimester and on final birth outcomes.

Conflict of Interest

None declared.

References

1. World Health Organization. WHO Recommendations for the Prevention and Management of Tobacco Use and Second-Hand Smoke Exposure in Pregnancy. n.d. Available from: https://www.who.int/publications/i/item/9789241506076 [Last accessed: 9/8/2025].
2. Ananth C V., Savitz DA, Luther ER. Maternal cigarette smoking as a risk factor for placental abruption, placenta previa, and uterine bleeding in pregnancy. Am J Epidemiol 1996;144(9):881–889; doi: 10.1093/OXFORDJOURNALS.AJE.A009022,.
3. Wang X, Gao X, Chen D, et al. The effect of active and passive smoking during pregnancy on birth outcomes: A cohort study in Shanghai. Tob Induc Dis 2024;22(July):1–7; doi: 10.18332/TID/188866.
4. Bruin JE, Gerstein HC, Holloway AC. Long-term consequences of fetal and neonatal nicotine exposure: a critical review. Toxicol Sci 2010;116(2):364–374; doi: 10.1093/TOXSCI/KFQ103.
5. Niu Z, Xie C, Wen X, et al. Placenta mediates the association between maternal second-hand smoke exposure during pregnancy and small for gestational age. Placenta 2015;36(8):876–880; doi: 10.1016/J.PLACENTA.2015.05.005.
6. Jaddoe VWV, Verburg BO, De Ridder MAJ, et al. Maternal smoking and fetal growth characteristics in different periods of pregnancy: the generation R study. Am J Epidemiol 2007;165(10):1207–1215; doi: 10.1093/AJE/KWM014.
7. Dempsey D, Jacob P, III, et al. Accelerated metabolism of nicotine and cotinine in pregnant smokers. J Pharmacol Exp Ther 2002;301(2):594–598; doi: 10.1124/JPET.301.2.594.
8. Demir R, Demir AY, Yinanc M. Structural changes in placental barrier of smoking mother. A quantitative and ultrastructural study. Pathol Res Pract 1994;190(7):656–667; doi: 10.1016/S0344-0338(11)80744-2.
9. Eskenazi B, Prehn AW, Christianson RE. Passive and active maternal smoking as measured by serum cotinine: the effect on birthweight. Am J Public Health 1995;85(3):395–398; doi: 10.2105/AJPH.85.3.395.
10. Wadi MAA, Al-Sharbatti SS. Relationship between birth weight and domestic maternal passive smoking exposure□. Eastern MediterraneanHealth Journal 2011;17(4).
11. Luo Y-J, Wen X-Z, Ding P, et al. Interaction between Maternal Passive Smoking during Pregnancy and CYP1A1 and GSTs Polymorphisms on Spontaneous Preterm Delivery. PLoS One 2012;7(11):e49155; doi: 10.1371/JOURNAL.PONE.0049155.
12. Newnham JP, Patterson L, James I, et al. Effects of maternal cigarette smoking on ultrasonic measurements of fetal growth and on Doppler flow velocity waveforms. Early Hum Dev 1990;24(1):23–36; doi: 10.1016/0378-3782(90)90003-2.
13. Remmer H. Passively inhaled tobacco smoke: a challenge to toxicology and preventive medicine. Arch Toxicol 1987;61(2):89–104; doi: 10.1007/BF00661366.
14. Parra-Saavedra M, Simeone S, Triunfo S, et al. Correlation between histological signs of placental underperfusion

and perinatal morbidity in late-onset small-for-gestational-age fetuses. Ultrasound in Obstetrics and Gynecology 2015;45(2):149–155; doi: 10.1002/UOG.13415,.

15. Yıldırım SB, Yılmaz KİA, Gulerman C. The Effect of Active and Passive Maternal Smoking During Pregnancy on the Uterine Artery Blood Flow and Obstetric Outcomes: A Prospective Study. Cureus 2023;15(2):e35270; doi: 10.7759/CUREUS.35270.