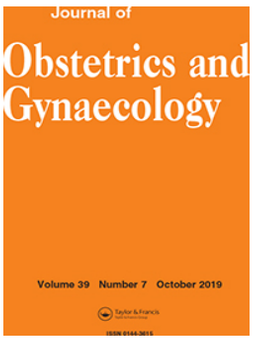

Journal of Obstetrics and Gynaecology

ISSN: 0144-3615 (Print) 1364-6893 (Online) Journal homepage: https://www.tandfonline.com/loi/ijog20

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To cite this article: Fusun Terzioglu, Handan Boztepe, Pinar Erkekoglu, Aslı Er Korucu, Belma Kocer-Gumusel & Omer Kandemir (2019) The effects of amniotic fluid and foetal cord blood cotinine concentrations on pregnancy complications and the anthropometric measurements of newborns, Journal of Obstetrics and Gynaecology, 39:7, 952-958, DOI: 10.1080/01443615.2019.1599834

To link to this article: https://doi.org/10.1080/01443615.2019.1599834

Published online: 19 Jun 2019.

JOURNAL OF OBSTETRICS AND GYNAECOLOGY
2019, VOL. 39, NO. 7, 952–958
https://doi.org/10.1080/01443615.2019.1599834

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ORIGINAL ARTICLE

The effects of amniotic fluid and foetal cord blood cotinine concentrations on pregnancy complications and the anthropometric measurements of newborns

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ABSTRACT

Our objective was determining the effects of amniotic fluid (AF) and fetal cord blood (FCB) cotinine concentrations on pregnancy complications and the anthropometric measurements in the newborns whose mothers underwent amniocentesis. This study was conducted as a case-control study, in Turkey. A total of 250 pregnant women with amniocentesis indication were recruited into the study and the cotinine levels in the AF and FCB were determined. A smoking habit did not statistically affect the incidence of pregnancy complications ($p>.05$). The birth weights of the newborns were negatively correlated with the AF cotinine levels. The incidences of low birth weight, low Apgar scores and RDS were positively correlated with higher levels of cotinine in AF and FCB. It is important for healthcare staff to provide training and consultancy services for the health improvement of pregnant women and the prevention of smoking during pregnancy.

IMPACT STATEMENT

- **What is already known on this subject?** The pre-pregnancy smoking habit usually continues during the pregnancy. A significant negative correlation was present between the foetal cord blood cotinine levels and the birth weight.
- **What do the results of this study add?** The anthropometric measurements of the newborns born from mothers with high AF cotinine levels were lower than newborns born from mothers with low amniotic fluid cotinine levels. Respiratory Distress syndrome is more often determined in newborns born from mothers with high AF cotinine levels.
- **What are the implications of these findings for clinical practice and/or further research?** Future studies should be performed to investigate the effects of cigarette smoking on the health problems, the growth characteristics and the neurological development of newborns and infants within the first year of life.

KEYWORDS

Smoking; cotinine; foetal cord blood; newborn complications; pregnancy complications; amniocentesis

Introduction

Smoking is identified as a 'bio-psychosocial intoxication state' by the World Health Organization (WHO) (WHO 2005). According to WHO (WHO 2013), 19% of the females are smokers (WHO 2013, 2017). In Turkey, the rate of smoking among females (≤15 years) is 15.2%. The rate of smoking among high school graduate females has been determined to be 27.4%. There is at least one smoker in 59.7% of homes; 21 million individuals are affected from passive smoking in Turkey (WHO 2017).

The smoking habit in women sometimes continues during pregnancy (Cosci et al. 2011). About 11.4–25.1% of smoking women continue to smoke during their pregnancy throughout the world, with similar rates in Turkey (Pickett et al. 2003; Center for Disease Control and Prevention (CDC) 2004; Lee et al. 2004; Doğu and Ergin 2008; Schneider et al. 2008; Terzioğlu and Yücel 2008; Turkish Republic Ministry of Health General Directorate of Primary Health Care 2012).

Cigarettes negatively affects the mother and newborn (Shea and Steiner 2008; Cosci et al. 2011). The nicotine and carbon monoxide in cigarette smoke can increase pregnancy complications [i.e. spontaneous abortion, ectopic pregnancy, placenta praevia, placental abruption, early membrane rupture (EMR) and premature birth] (Himmelberger et al. 1978; Armstrong et al. 1992; Wang et al. 1997; Bernstein et al. 2005; Chertok et al. 2011; Cosci et al. 2011; Slaughter et al. 2011). Prenatal nicotine exposure can cause intrauterine growth retardation, prematurity, low birth weight, changes in

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brain structure/function and congenital anomalies (CDC 2004; Ginzel et al. 2007; Ingvarsson et al. 2007; Stroud et al. 2009; Gray et al. 2010; Salmasi et al. 2010; Bublitz and Stroud 2012; Milnerowicz-Nabzdyk and Bizoń 2014). More pregnancy complications (i.e. hypertension, EMR, gestational diabetes, placental problems) are observed in pregnant women with high amniotic fluid (AF) cotinine levels (Lindblad et al. 1988; Bernstein et al. 2005; Ashford et al. 2010; Gray et al. 2010; Zhu et al. 2014; Han et al. 2015; Mattsson et al. 2016). The anthropometric measurements of newborns from mothers with high AF cotinine levels are lower than the newborns of mothers with low AF cotinine levels (Ingvarsson et al. 2007; Ashford et al. 2010). Respiratory distress syndrome (RDS) and/or low Apgar scores are more often determined in newborns with high AF cotinine levels (Ingvarsson et al. 2007; Ashford et al. 2010).

In regards to the data, we aimed to determine effects of active/passive smoking during pregnancy on the health indicators of the newborns. We had three hypotheses:

1. More pregnancy complications (such as hypertension, premature activity, EMR, gestational diabetes, placenta problems) are seen in pregnant women with a high cotinine level in the AF.
2. The anthropometric measurements (such as the length, weight and head circumference) of the newborns born from mothers with high AF cotinine levels are lower than in newborns born from mothers with lower AF cotinine levels.
3. RDS and/or low Apgar scores are more often determined in newborns born from mothers with high AF cotinine levels.

The cotinine levels in the AF and in foetal cord blood (FCB) were measured as the biomarkers of nicotine exposure. Correlations between the cotinine levels and pregnancy and the complications in newborns were also evaluated.

Material and methods

Study design and sampling

This study was designed as a case control study on healthy pregnant women (18–42 years; mean age: 31.75 ± 6.57 years) who underwent amniocentesis (between 14 and 20 weeks of gestation) at the perinatology unit of a state hospital in Ankara. The mothers were met by the same physician and they were kindly informed about the suspicion of the presence of a genetic disorder. They were gently informed about the concept of the study (AF and FCB withdrawals, the face-to-face questionnaire and their willingness to give information on their smoking habits) and then the physician asked whether they wished or not to join this study. A written informed consent (on all of the procedures performed on the study, including that had been obtained from all of the subjects' AF withdrawal and FCB withdrawal) was obtained from all of the study's participants. Women who had infections (bacterial, viral or fungal) or a prior pathological condition (diabetes, obesity, hypertension, neurological disorders) were excluded from the study. Moreover, women who did not give their consent for either AF or FCB withdraw were not included.

Amniocentesis was usually performed due to the suspicion of Down's syndrome (in 85.2%) or any other genetic disorder. Amniocentesis was performed by using a standard procedure. Before the physician-in-charge started the procedure, a local anaesthetic was given to the mother in order to relieve the pain felt during the insertion of the needle used to withdraw the fluid. After the local anaesthetic took effect, a needle was usually inserted through the mother's abdominal wall, then through the uterus wall and finally into the amniotic sac. With the aid of ultrasound-guidance, a physician punctured the sac in an area away from the foetus and extracted ~15–20 mL of AF.

Ethical approval was obtained from Hacettepe University's (HEK09/258-24) and Zübeyde Hanım Etlik Women's Health and Disease, Teaching and Research Hospital's Human Ethics Committees (2011/144/8). There were no differences between the women concerning socio-economic and cultural characteristics (monthly income, downtown area living, graduation from primary/secondary/high schools).

The pregnant women were grouped as:

1. Non-smokers (husband and wife were non-smokers or former smokers),
2. Passive smokers (wife was a non-smoker, husband was a smoker) and
3. Smokers (current/regular or occasional smokers, husband was a smoker or non-smoker).

The participants were communicated with by fortnightly phone calls during the pregnancy. The FCB samples were taken just after the birth.

Data collection

A face-to-face questionnaire was applied. AFs were collected from a total of 250 pregnant women (102 smoking, 148 non-smoking; 36 women stopped smoking after pregnancy; 187 of these women gave birth at the study hospital; 45 gave birth at other hospitals). FCB could only be obtained from 82 women (47 smoking, 25 not smoking). The samples were transferred in a cold chain to the Hacettepe University Toxicology Department and kept at –80 °C until analysis.

Cotinine analysis

Cotinine is the predominant metabolite of nicotine. Half-life of cotinine ($t_{1/2}$) is ~17 h while $t_{1/2}$ of nicotine is ~2 h. Because of its long $t_{1/2}$ and constant concentrations, cotinine is usually chosen for the determination of nicotine exposure (Benowitz 1996; Moran 2012).

The enzyme-linked immunosorbent assay (ELISA) is a commonly used analytical biochemistry assay, first described by Weiland (1978). The assay uses a solid-phase enzyme immunoassay (EIA) to detect the presence of a ligand (commonly a protein) in a liquid sample using antibodies directed against the protein to be measured. The technique essentially requires any ligating reagent that can be immobilised on the

solid phase, together with a detection reagent that can particularly bind and use an enzyme to generate a quantitative signal.

In between the washes, only the ligand and its specific binding counterparts can remain bound or 'immunosorbed' by antigen–antibody interactions to the solid phase, while the non-specific or unbound components are washed away. ELISA plates have the reaction products immunosorbed on the solid phase which is part of the non-reusable plate. ELISA can be performed in three different forms: direct, sandwich and competitive. In competitive ELSA, unlabelled antibody is incubated in the presence of its antigen (sample). These bound antibody/antigen complexes are then added to an antigen-coated well. Later, the plate is washed, so unbound antibodies are removed and secondary antibody, specific to the primary antibody, is added. This second antibody is coupled to the enzyme.

At the end, a substrate is added, and remaining enzymes elicit a chromogenic or fluorescent signal and the reaction is stopped to prevent the eventual saturation of the signal. Solid-phase competitive ELISA cotinine kits were obtained from Calbiotech (Spring Valley, CA) and used throughout the experiments.

Samples (10 µl), standards (10 µl) and cotinine enzyme conjugate (horseradish peroxidase, HRP) were applied to anti-cotinine antibody-coated wells. A plate was agitated and incubated for 60 min at 25°C. The cotinine competed with the HRP. The unbound cotinine and HRP were later washed off. Then, substrate (100 µl) was added to each well, and the plate was incubated for 30 min. Later, a stop solution (100 µl) was added to the wells. Colour intensity (inversely correlated with cotinine concentrations) was measured at 450 nm. A standard curve was drawn using a special computer programme (RidaWin, Darmstadt, Germany) and the cotinine amounts were calculated. The sensitivity of the test was 1 ng/mL. Specificity was evaluated with antisera for cross-reactivity. The cross-reactivity values for nicotine, nicotinamide and nicotinic acid were <1%.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences 10.0 (SPSS Inc., Chicago, IL). The distributions of values were analysed by Kruskal–Wallis variance. The data was expressed as the mean ± standard deviation (SD) for normal distributions and as the median (minimum–maximum) for abnormal distributions. The comparison between two parametric values was determined by using the Student's *t*-test. Two nonparametric values were compared by using the Mann–Whitney *U*-test. The categorical variables were compared by using Pearson's Chi-square test or the Fisher Chi-square test. $p < .05$ was considered as being statistically significant.

Results

About 32.8% of pregnant women were aged ≥36 years; 36% were high school graduates and 72.4% did not work. The body mass index (BMI) was >18.5 in 13.6% of the subjects and over 30 in 3.6% of the subjects. Cotinine levels in the AF and the smoking mothers' characteristics are given in Table 1.

The pregnant women were sub-grouped as follows based on AF cotinine levels (Köhler et al. 2007; Ness et al. 2008):

- non-exposed group: cotinine levels in AF ≤ 15 ng/mL,
- low-exposed group: cotinine levels in AF between 16 and 99 ng/mL and
- heavily exposed group: cotinine levels in AF ≥ 100 ng/mL.

We observed 82.2% of pregnant women were non-exposed to cigarette smoke; 9.4% were low-exposed and 8.4% were heavily exposed (Figure 1). About 53.6% of the pregnant women stated that they had never smoked while 14% stated they smoked occasionally, 24.4% were still smoking during their pregnancy and 64.6% of these women noted that they smoked every day. Twenty-five percent of the women had stopped smoking after the pregnancy. About 34.8% of the subjects stated at least one person smoked nearby and the husband was the smoker in 88.9% of the cases. The cotinine levels in the AF and the pregnancy complications are presented in Table 2.

The mean birth weight was 3262.45 g in infants born from non-exposed mothers. The mean birth was found to be

Table 1. Cotinine levels in the amniotic fluid and smoking characteristics of the mothers.

		Cotinine levels			Statistical analysis		
	N	Median	Min.	Max.		*p*	Difference
Smoking status							
Never smoked	96	0.01	0.001	120.34	74.558*	.001	
Stopped smoking	16	0.55	0.003	139.84			
Occasionally smoking	32	0.06	0.008	122.59			
Currently smoking	59	1.32	0.003	254.34			1–2.3.4
Frequency of smoking							
Everyday (~5 cigarettes per day)	58	2.74	0.003	254.34		.001	
Per week	33	0.05	0.008	106.62	3.438**		
Living in an environment where cigarette smoke is present							
Yes	77	0.13	0.001	254.34		.091	
No	126	0.04	0.002	167.74	1.689**		
Existence of person who smoke at home							
Yes	79	0.13	0.001	254.34		.064	
No	124	0.04	0.002	167.74	1.849**		

*Kruskal–Wallis variance analysis.
**Mann–Whitney *U*-test.

3086.32 g in infants from low-exposed mothers and 3004.12 g born from heavily exposed women. There is no statistical difference between the birth weights of the babies born to mothers with low and high nicotine exposure.

Only 59 of the FCB samples were eligible for measurement of cotinine levels (due to haemolysis, undetectable cotinine levels, etc.). The newborns were sub-grouped as follows, based on the cotinine levels of FCB (Milnerowicz-Nabzdyk and Bizoń 2014):

- low-exposure group: cotinine levels ≤15 ng/mL and
- high-exposure group: cotinine levels >15 ng/mL.

The mean length of newborns in low-exposure group was 48.96 and 47.75 cm in high-exposure group (Table 3; $p > .05$). The mean weight of newborns was 3231.37 g in low-exposure group and 3018.75 g in high-exposure group (Table 3; $p > .05$). In low-exposure group, mean head circumference of newborns was 34.96 cm while it was 34.63 cm in high-exposure group (Table 3; $p > .05$). There is no statistical difference between the lengths of the babies born to mothers with low and high nicotine exposure.

There was no statistically significant correlation between the AF cotinine levels and Apgar scores (at first minute) in the newborns ($p > .05$). However, a statistically significant correlation was observed between the AF cotinine levels and RDS in the newborns (Table 4). The Apgar score (at first minute) was ≥8 in 94.6% of the newborns and ≤7 in 5.4% of the newborns. RDS was observed in 3.6% of the babies, while meconium aspiration syndrome and infection complications were present in 0.8% of the newborns. No apnoea, asphyxia or atelectasis were determined.

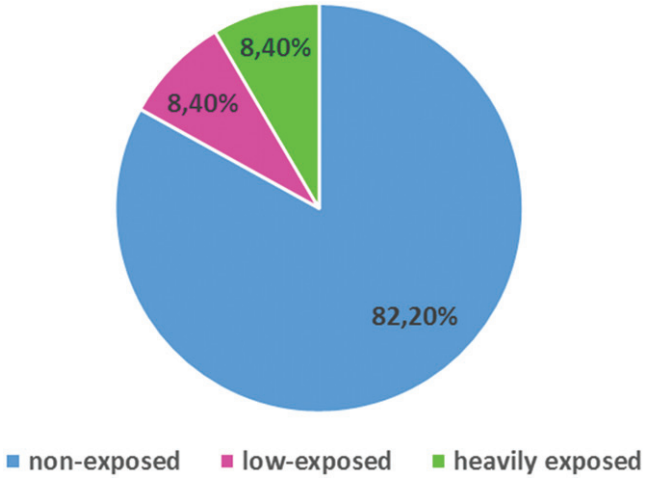

Figure 1. Distribution of cotinine levels in amniotic fluid of pregnant women. Non-exposed group: cotinine levels in AF≤15 ng/mL. Low-exposure group: cotinine levels in AF between 16 and 99 ng/mL. Heavily exposed group: cotinine levels in AF ≥ 100 ng/mL.

Discussion

Smoking during pregnancy negatively affects the health of the mother and the foetus (Himmelberger et al. 1978; Luck et al. 1985; Armstrong et al. 1992; Wang et al. 1997; Bernstein et al. 2005; Wickström 2007; Chertok et al. 2011; Cosci et al 2011). The major adverse health effects of smoke exposure can be stated as follows (Wickström 2007).

- Vasoconstrictor effect of nicotine can cause disruption of placental function, insufficient oxygen delivery to the uterus and a lower amount of nutrient transfer to the foetus.
- Active/passive smoke exposure can lead to placental problems.
- Carbon monoxide can lead to decreases in foetal oxygenation.
- Smoking slows down/stops the vascularisation process, delays the growth and development of embryo.

In this study, AF cotinine levels were found to be ≤15 ng/mL in >80% of pregnant women, indicating a very low/no exposure to smoke. In ~9% of women, the AF cotinine levels were between 16 and 99 ng/mL (mild exposure) and in >8%

Table 2. Cotinine levels in the amniotic fluid and pregnancy complications.

		Cotinine levels (ng/mL)			Statistical analysis	
	N	Median	Min.	Max.	*Z**	*p*
Spontaneous abortion[a]						
Not present	202	0.42	0.001	254.34	–	–
Present	1	0.62	106.62	106.62		
Placental abnormalities[a]						
Not present	201	0.043	0.001	254.34	–	–
Present	2	0.018	0.002	0.034		
Premature birth[a]						
Not present	200	0.045	0.001	254.34	–	–
Present	3	0.011	0.003	0.019		
Stillbirth[a]						
Not present	202	0.043	0.001	254.34	–	–
Present	1	0.003	0.003	0.003		
Gestational diabetes[a]						
Not present	196	0.043	0.001	254.34	0.023*	.982
Present	7	0.024	0.007	157.74		
Hypertension[a]						
Not present	188	0.045	0.001	254.34	0.731	.465
Present	15	0.038	0.002	179.73		

*Mann–Whitney *U*-test.
[a]As the number of subjects who had spontaneous abortion, placental abnormalities, premature birth and stillbirth is quite low compared to the subjects without these complications is quite low, a statistical analysis could not be performed.

Table 3. Foetal cord blood cotinine levels of the newborns and anthropometric measurements.

FCB cotinine level (ng/mL)	Mean length (cm)	Mean weight (g)	Head circumference (cm)
Low-exposure group (FCB cotinine $\leq$ 15 ng/mL)	48.96	3231	34.96
High exposure group (FCB cotinine $>$ 15 ng/mL)	47.75	3018	34.63

FCB: foetal cord blood.

Table 4. Amniotic fluid cotinine levels, Apgar scores (first minute) and respiratory distress syndrome.

AF cotinine levels (ng/mL)	Apgar score	RDS
	$\leq$7, 5.7% in total	4.4% present, in total
Non-exposed group (AF cotinine $\leq$ 15 ng/mL)	5.8%	2.4% present
Low exposed group (AF cotinine 16–99 ng/mL)	5.3%	15.8% present
Heavily exposed group (AF cotinine $\geq$ 100 ng/mL)	5.9%	11.1% present
	$\leq$8, 94.3% in total	95.6% not present, in total
Non-exposed group (AF cotinine $\leq$ 15 ng/mL)	94.2%	97.6% not present
Low exposed group (AF cotinine 16–99 ng/mL)	94.7%	84.2% not present
Heavily exposed group (AF cotinine $\geq$ 100 ng/mL)	94.1%	88.9% not present

AF: amniotic fluid; RDS: respiratory distress syndrome.

of the women, AF cotinine levels were >100 ng/mL (high exposure). The incidence of pregnancy complications were not correlated with AF cotinine levels ($p > .05$). Therefore, our first hypothesis was not accepted. The limited number of pregnant women in the mild or high exposure groups may have influenced these results, along with cofounding factors. Fantuzzi et al. (2007) reported that exposure to active/passive smoking increased preterm birth. Mutsaerts et al. (2014) indicated that smoking in pregnancy could increase the risk of gestational diabetes, hypertension, preterm birth and low birth weight. Hammoud et al. (2005) observed that high cigarette smoke exposure could decrease preeclampsia incidence and cause intrauterine growth retardation. Aliyu et al. (2011) observed a correlation between smoking and placental abruption, *placenta praevia*, stillbirth and preterm birth. In addition, newborns whose parents smoked had higher birth defects versus newborns with non-smoker parents. Jauniaux and Burton (2007) reported that newborns whose mothers are exposed to passive cigarette smoke seem to be more affected from its toxic effects.

Prenatal smoke exposure is suggested to negatively affect anthropometric measurements (Jauniaux et al. 1999; Zenzes et al. 1999; Ginzel et al. 2007; Jaddoe et al. 2007; Jauniaux and Burton 2007; Himes et al. 2013; Iñiguez et al. 2013; Milnerowicz-Nabzdyk and Bizoń 2014). High smoke exposure in all trimesters causes unwanted effects on the foetus (England et al. 2001; Ingvarsson et al. 2007; Tiesler and Heinrich 2014). We found that the birth weight of the newborns were negatively correlated with the AF cotinine levels. Our second hypothesis was partially accepted, as there was only a significant relationship between birth weight and AF cotinine levels ($p < .05$). A study conducted in UK showed that the birth weights of the newborns, whose mothers were exposed to passive cigarette smoke during pregnancy, were found to be 40–70 g lower than unexposed newborns. Kharrazi et al. (2004) reported increased rates of low birth weight, preterm activity and foetal death were observed in newborns born from women who had high maternal serum cotinine levels due to second-hand smoke. El-Mohandes et al. (2009) reported that high cotinine levels in the sputum of mothers during pregnancy and right before birth were negatively associated with birth weight. We observed that cotinine levels did not show associations with the length and head circumference of newborns. Similarly, in a large-scale study with 1175 subjects, Bolat et al. reported in 2012 that smoking during pregnancy only affected the weight of the newborn.

The effects of active/passive smoking of the mother on the health of the foetus or infant have been widely studied (Wisborg et al. 2001; Ginzel et al. 2007; Aycicek and Ipek 2008; Stroud et al. 2009; Gray et al. 2010; Salmasi et al. 2010; Aycicek et al. 2011; Bublitz and Stroud 2012; Bertani et al. 2015). Smoking in pregnancy has been found to cause genetic and congenital problems in newborns, and the development of many childhood chronic diseases (Lindblad et al. 1988; Iñiguez et al. 2013; Møller et al. 2014; Mattsson et al. 2016). There was not a statistically significant association between the AF cotinine levels and the Apgar scores of the newborns. However, the rate of RDS in the newborns of pregnant women with low AF cotinine levels was significantly lower than in the newborns whose mothers had higher AF cotinine levels. We therefore partially accepted the third hypothesis. Hammoud et al. (2005) found asphyxia and the intubation requirement of newborns whose mothers smoked 10 cigarettes/day, were higher versus the newborns with non-smoker mothers. In this study, RDS was observed in 3.6% of the newborns.

This study has some limitations: the most important restraint was raised from obtaining the limited number of FCBs, as some women recruited in the study gave birth at different hospitals or did not give any information to the study researchers where and when they gave birth. In addition, cotinine levels of nine FCB samples could not be measured due to haemolysis. Moreover, the cotinine levels in 14 samples (12 in the control group and 2 in the smoking group) were under the detection levels. Two of the samples had very high cotinine levels and were above the detection limits. Due to these hitches, cotinine analysis could be

conducted on 59 FCB samples. Although the second and third hypotheses were partially accepted, it is impossible to reach to a clear conclusion, due to the relatively low number of subjects recruited into the study.

Despite these limitations, our results support other reports that smoking negatively affects the health of newborns. In addition, our findings suggest that smoking negatively affects the birth weight. In conclusion, epidemiological studies with a higher number of subjects are needed to investigate the effects of cigarette smoking on the health problems, growth characteristics and neurologic development of newborns and infants within their first year of life.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by Hacettepe University's Research Fund [Project Number: 01001401002 (5213)].

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