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# Exposure to Environmental Tobacco Smoke during Pregnancy Restrain the Antioxidant Response of their Neonates

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## Abstract

**Purpose:** Smoking during pregnancy has several effects and risks on the neonates. The aim is to assess the effects of exposure to environmental tobacco smoke duringpregnancy on the antioxidant status of their neonates.

**Design:** In cord blood samples of 116 healthy newborns which were classified into groups according to mothers smoking status (active, passive or non-smoker), the activities of paraoxanase 1 and aryl esterase, concentrations of free sulfhydryl groups and total antioxidant response were studied using appropriate methods.

**Results:** Different parameters indicating antioxidant status had similar values in cord blood of term and preterm neonates of active or passive smoke or non-smoker mothers. Only, concentrations of total antioxidant response were statistically different between cord blood of neonates of active or passive smoker mothers and cord blood of term or preterm neonates of non-smoker mothers (1.12 ± 0.1, 1.10 ± 0.08 and 1.28 ± 0.12 mmol trolox equivalent/L, for term neonates, 0.95 ± 0.0, 1.07 ± 0.13 and 1.22 ± 0.02 mmol trolox equivalent/L, for preterm neonates, respectively).

**Conclusions:** Neonates of active or passive smoker mothers have decreased antioxidant levels in cord blood and may be exposed to an oxidative stress greater.

**Keywords:** Antioxidant; Smoke; Pregnancy; Cord blood; Neonate

## Introduction

Exposure to environmental tobacco smoke (ETS) is a major threat to public health [1]. Passive smoking comprises side-stream smoke emitted from the smouldering tobacco between puffs and exhaled mainstream smoke from the smoker. The detrimental effects associated with maternal smoking during pregnancy can occur through several different mechanisms, both indirectly by affecting placental tissues and umbilical artery blood flow as well as directly via placental transfer. There are numerous potentially harmful chemicals in cigarette smoke associated with adverse effects during pregnancy, in particular nicotine, carbon monoxide, tar, benzene and heavy metals such as lead and cadmium [2].

Nicotine and carbon monoxide may have adverse effects on human body. Nicotine passes by the placenta and can be detected in the foetal circulation and amniotic fluid in which its concentrations are 15% and 88% higher than maternal plasma, respectively. The most current metabolic compound of nicotine is cotinine which has a longer half-life time and which reaches on higher levels in the maternal plasma than nicotine. The actions of nicotine are a predictable decrease in uterine artery blood flow, variable changes in umbilical artery flow, and variable changes in foetal oxygenation and acid-base balance; also, a decrease in foetal heart rate and an increase in mean arterial pressure [3-5].

Carbon monoxide also passes by placenta and is detected in the foetal circulation, at level 15% higher than maternal plasma. The formation of carboxyhemoglobin shifts the oxygen dissociation curve to the left and results by a decrease in the availability of oxygen to foetal tissues [6].

Other than cotinine in the content of cigarette smoke exists gases and compound tar particles which have oxidant and pro-oxidants effects and capable to produce reactive oxygen species [7,8]. Its enhanced production creates oxidative stress and results by the oxidation of lipids, induction of DNA single-strained breakage, inactivation of certain proteins and the disruption of biological membranes [9-11]. Increased oxidative stress, increases lipid peroxidation and reduces blood levels of antioxidants, play a major role in the pathogenesis of several smoking-related disease [1,12].

Cigarette smoking causes oxidative stress in pregnant women and may have a similar effect on foetus. Although the effect of smoking on adults is well known, the effects of passive smoking in infants are

understood less [13]. Published studies on the oxidative effects of passive smoking are based about children and adults, than infants [7,14].

One part; early infancy is a time of oxidative stress due to difficulty of adapting to ambient oxygen, the purpose of this study was to prospectively investigate the effects of maternal ETS exposure during pregnancy on the prevalence and severity of the changes on the antioxidant response of their neonates.

## Patients and Methods

### Study design

The study was conducted as a prospective observational study of antioxidant response of healthy newborns born in Firat University Hospital. The study protocol was approved by The Research Committee of Firat University and by The Regional Ethic Committee. Written permit were taken from each of the families of the newborns. Gestational age was determined from the date of last menstrual period and confirmed by using the New Ballard Score [15] and those less than 37 weeks were classified as preterm and those between 37-41 weeks as term. A detailed smoke history of pregnant women was obtained (smoking or not, how many cigarettes a day, another person smoking near them e.g.) and gestational problems were evaluated. Pregnant women were classified into three groups as active smoker (more than ten cigarettes a day), passive smoker (exposed to passive smoking at least ten cigarette per day during pregnancy in their homes) and non-smoker (never been exposed to active or passive smoking), and this classification was summarized in Table 1. The exclusion criteria of this study were being active and passive smoker at the same time or smoking actively or passively less than ten cigarettes per day and having preeclampsia, hypertension or infection.

### Cord blood samples

Cord blood samples were withdrawn into heparinised tubes and plasma was separated by centrifugation at 3.000 rpm for 10 minutes. The plasma samples were stored at -70°C until required for analysis. Activities of paraoxanase (PON1) and aryl esterase (ARE), concentrations of free sulfhydryl groups (SH) and total antioxidant response (TAR) were studied in cord blood sample obtained at birth and preserved in EDTA additioned tubes.

### Measurement of the activities of PON1 and ARE [16]

Activity of paraoxonase was determined using paraoxon as a substrate and measured by increases in the absorbance at 412 nm due to the information of 4-nitrophenol as already described. Briefly, the activity was measured at 25°C by adding 50 µl of samples to 1 ml Tris-HCl buffer (100 mM at pH 8.0) containing 2 mM $CaCl_2$ and 5.5 mM of paraoxon. The rate of generation of 4-nitrophenol was determined at 412 nm. Enzymatic activity was calculated using the molar extinction coefficient 17 100 M-1$cm^{-1}$.

Activity of aryl esterase was measured spectrophotometrically. The assay contained 1 mM of phenylacetate in 20 mM Tris-HCl at pH 8. The reaction was started by the addition of plasma and the increase in absorbency was recorded at 270 nm as already described. Blanks were included to correct for the spontaneous hydrolysis of phenylacetate. Enzyme activity was calculated using the molar extinction coefficient of 310 $M^{-1}cm^{-1}$.

| | Active smoker | | Passive smoker | | Nonsmoker | |
|---|---|---|---|---|---|---|
| | Preterm | Term | Preterm | Term | Preterm | Term |
| Number | 12 | 20 | 10 | 28 | 14 | 32 |
| Birth Weight (g) | 1688 ± 528 | 3114 ± 305 | 1545 ± 261 | 3045 ± 304 | 1500 ± 360 | 3177 ± 426 |
| Gestational period (week) | 33.3 ± 2.1 | 39.1 ± 0.7 | 34.5 ± 0.7 | 39.5 ± 1.0 | 34.3 ± 2.5 | 39.3 ± 0.8 |

**Table 1:** Demographic characteristics of newborns.

### Measurement of SH groups

Free SH of plasma samples were assayed according to the method of Elman [17] as modified by Hu et al. [18]. Briefly, 1 ml of buffer containing 0.1 M Tris, 10mM EDTA at pH 8.2 and 50 µl plasma were added to cuvettes, followed by 50 µl of 10 mM dithiobis (nitrobenzoate) in methanol. Blanks were run for each sample as a test, but there was no dithiobis (nitrobenzoate) in the methanol. After incubation for 15 min at room temperature, sample absorbance was read at 412 nm on Cecil 3.000 spectrophotometer. Sample and reagent blanks were subtracted. The concentration of SH was calculated using reduced glutathione as free SH Standard [18].

### Measurement of the total antioxidant status of plasma

The total antioxidant status of the plasma were measured using a novel automated colorimetric measurement method for the total antioxidant response developed by Erel [19,20]. In this method the hydroxyl radical, the most potent biological radical, is produced by the Fenton reaction, and reacts with the colourless substrate O-dianisidine to produce the dianisyl radical, which is bright yellowish-brown in colour. Upon the addition of a plasma sample, the oxidative reactions initiated by the hydroxyl radicals present in the reaction mix are suppressed by the antioxidant components of the plasma, preventing the colour change and thereby providing and effective measure of the total antioxidant capacity of the plasma and pleural fluids. The assay results are expressed as mmol Trolox eq/L and the precision of this assay is excellent being lower than 3% [21].

### Statistics

All statistical analysis was performed using SPSS for Windows version 11.0 (SPSS, Chicago, IL, USA). Differences in the serum parameters between active smoker, passive smoker and non-smoker were analyzed by one way ANOVA with Tukey's significant difference multiple comparison test. For determination of the differences into term and preterm newborn groups Mann-Whitney U and Kruskal

Wallis tests were used. The data were expressed as mean ± S.D. and p values of less than 0.05 were considered to be significant.

| | Active smoker | Passive smoker | Non-smoker | p |
|---|---|---|---|---|
| PON1 activity (U/L) | | | | |
| Preterm | 14.81 ± 2.74 | 17.44 ± 5.51 | 19.40 ± 7.09 | <0.05 |
| Term | 19.18 ± 5.87 | 19.79 ± 4.54 | 21.50 ± 7.42 | NS |
| p | <0.05 | NS | | |
| ARE activity (U/L) | | | | |
| Preterm | 420.59 ± 64.72 | 425.41 ± 35.40 | 435.83 ± 36.71 | NS |
| Term | 426.34 ± 66.83 | 418.21 ± 51.23 | 448.33 ± 41.17 | NS |
| p | NS | NS | NS | |
| SH level (U/L) | | | | |
| Preterm | 0.39 ± 0.01 | 0.39 ± 0.02 | 0.40 ± 0.02 | NS |
| Term | 0.42 ± 0.03 | 0.42 ± 0.03 | 0.43 ± 0.03 | NS |
| p | NS | NS | NS | |
| TAR levels (mmol TroloxEq/L) | | | | |
| Preterm | 0.95 ± 0.03 | 1.07 ± 0.13 | 1.22 ± 0.02 | <0.05 |
| Term | 1.12 ± 0.12 | 1.10 ± 0.08 | 1.28 ± 0.12 | <0.05 |
| p | <0.05 | NS | NS | |

**Table 2:** Antioxidant status in all newborns.

## Results

Activities of PON1 and ARE, concentrations of SH and TAR in cord blood samples of term or preterm neonates of active, passive or non-smoker mothers were summarized in Table 1. Activities of PON1 and ARE, concentrations of SH and TAR were higher in cord blood of term neonates than preterm neonates of non-smoker mothers and this data was not statistically significant (NS).

Activity of PON1 was statistically different between cord blood of preterm neonates of active smoker and non-smoker mothers (14.81 ± 2.74 and 19.40 ± 7.09 U/L, $p<0.05$) and not statistically different between cord blood of term neonates. Activities of ARE and concentrations of SH were not statistically different between term or preterm neonates of all mothers. Concentrations of TAR were significantly higher in cord blood of term and preterm neonates of active or passive smoker than non-smoker mothers (1.12 ± 0.12 and 1.10 ± 0.08 versus 1.28 ± 0.12 mmol trolox equivalent/L, for term neonates, 0.95 ± 0.03 and 1.07 ± 0.13 versus 1.22 ± 0.02 mmol trolox equivalent/L, for preterm neonates, respectively $p<0.05$). All these data is summarized in Table 2.

## Discussion

Nicotine, major part of the smoke, damages the developing brain by altering the formation, survival and differentiation of brain cells and eliciting deficits in survival and behavioural performance [22,23]. Free-radicals induce directly or indirectly oxidative stress in the body and the major cause is exposure to ETS [2,24]. Reactive oxygen species such as superoxide radical anion, hydroxyl radical and hydrogen peroxide are produced in metabolic and physiological processes and harmful oxidative effects of reactive oxygen species are controlled by exogenous antioxidant such as vitamins E and C and also by endogenous antioxidants such as scavenger enzymes (superoxide dismutase and glutathione peroxidase), bilirubin and uric acid. Under some condition, increases in oxidants and decreases in antioxidants cannot be prevented, and the oxidative/antioxidative balance shifts towards the oxidative status [5]. Only TAR may reflect the antioxidant status of plasma, because antioxidants effects are additive [20,25,26].

Total antioxidant capacity shows antioxidant characteristic of all plasma antioxidants. Total antioxidant response and total antioxidant status is used to total antioxidant capacity's synonym. It was more useful to evaluate TAR than each antioxidant active measurement. For this purpose, a lot of new methods have been developed recently. Total radical trapping antioxidant parameter, oxygen radical absorbance capacity and ferric reducing antioxidant power are colorimetric methods to evaluate total antioxidant capacity [19,20,27].

Albumin, uric acid, bilirubin and ascorbic acid are the major antioxidant components of plasma. Total antioxidant capacity represents practically all of them and is reduced in chronic inflammation and similar in smoking [7,19,20]. The results of the study realised by Fayol et al. [28] show that maternal and neonatal antioxidant status is affected by active or passive exposure to tobacco smoke during pregnancy. The elevations of antioxidants parameters in these mothers and in their neonates may reflect an adaptation process to oxidative stress. In our present study; concentrations of TAR were lower in cord blood samples of neonates of active smoker mothers than neonates of non-smoker mothers.

Exposure to environmental tobacco smoke of pregnant women and infants is a health problem and can affect the developing brain and cardiovascular system. Concentrations of foetal nicotine metabolites may be similar in active or passive smoker mothers [21]. Aycicek et al. [7] found that passive maternal smoking has a negative effect on the antioxidant system in infants, based on a higher oxidative stress index and lower total antioxidant capacity, and lower plasma vitamin C and thiol concentrations. In the present study; concentrations of TAR were significantly lower in cord blood of term neonates of passive smoker mothers than non-smoker mothers. But, this difference was not significant in cord blood of preterm neonates of passive smoker mothers.

Chelchowska et al. [29] reported that effect of tobacco smoking during pregnancy on oxidative damage and antioxidant defence in matched samples of maternal blood and cord blood. Total antioxidant status positively correlated with concentrations of uric acid and vitamin E in non-smoking and smoking mothers as well as their newborns. Tobacco smoke enhances lipid peroxidation and depletes antioxidant potential in the plasma of pregnant women and umbilical cord blood. Therefore smoking during pregnancy may stimulate free radical damage in the mother and the growing fetus [29]. Human PON1 is an enzyme involved in vasodilatation and thrombosis. Disruption of blood blow through the placenta could be part of the pathophysiological mechanism leading to preterm delivery [30]. Smoking was associated with reduced serum PON1 [31]. In this study; activities of PON1 were lower in cord blood of preterm neonates than term neonates, and in cord blood of preterm neonates of active smoker mothers than passive or non-smoker mothers, but this difference was

not statistically significant. Also, activities of ARE were lower in cord blood of preterm neonates of active smoker mothers than passive or non-smoker mothers, but not significant.

It has been suggested that preterm neonates have a relative glutathione deficiency in proportion to the degree of prematurity. One possible cause is developmentally deficient liver cystathionase activity which impedes cysteine production from methionine via the transsulphuration pathway [32]. In this study; concentrations of SH were lower in cord blood of preterm neonates than term neonates. Similarly, activities of PON1 and ARE, and concentrations of TAR were higher in cord blood of term neonates. Not only has the production of these antioxidant enzymes increases during late gestation, also the transfer of these antioxidants as vitamin E, C, beta carotene across the placenta increases [33]. Titova et al. [34] reported that the effects of active and passive maternal smoking on umbilical cord serum levels of vitamin A and vitamin E were examined. Active and passive maternal smoking behaviour during pregnancy increases the fetal demand for antioxidant compounds in order to counteract the oxidative burden by cigarette smoke. This would reduce the availability of vitamins A and E for fetal maturation, which is critical in as much as both compounds are indispensable for the developing fetus [34]. Titova et al. [34] shown that active and passive smoking to be detrimental for the developing fetus.

The mechanism of the negative effects of mother smoking on neonates was not known clearly. Only, a lot of disease due to smoking has been determined [35]. Rossner et al. [36] reported that oxidative damage to macromolecules may have numerous negative healthconsequences. In their studies showed higher lipid peroxidation in newborns than in mothers, close correlationof analyzed oxidative stress markers between newborns and mothers, and a relationship between oxidative stress and induction of DNA adducts [36]. Aycicek et al. [37] reported that study's was to assess the influence of active and passive maternal smoking on placenta total oxidant/antioxidant status in term infants. Their studies, placenta, cord blood, and the maternal peripheral total antioxidant capacity (TAC) levels were significantly lower in the active smokers compared with the controls ($P<0.001$), while total oxidant status (TOS) and oxidative stress index (OSI) levels were significantly higher in the active and passive smokers than in the controls ($P<0.001$). A positive significant correlation was found between active maternal smoking and placenta TOS and OSI levels ($P<0.016$), and a significant negative correlation was found between number of cigarettes exposed to and birthweight and head circumference ($P<0.05$). In this their studies, active or passive maternal smoking is associated with important alterations in oxidant and antioxidant balance in fetal placental tissue and causes potent oxidative stres [37]. In our study, effects of active or passive smoking during pregnancy was determined as similar on the antioxidant status of preterm and term neonates. Only, concentrations of TAR, as an indicator of total antioxidant status, were significantly lower in cord blood of neonates of active or passive smoker mothers.

In conclusion, on one hand neonates of active or passive smoker mothers have decreased antioxidant concentrations and on the other hand the neonatal period is a time of oxidative stress due to the difficulty of adaptation. Neonates of active or passive smoker mothers are most exposed to oxidative stress which has been implicated in the etiopathogenesis of over 100 disorders.

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