

## Influence of maternal cigarette smoking during pregnancy on neonatal serum folate levels

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### Abstract

**Purpose** Folate is an essential micronutrient for fetal development because of its role in de novo synthesis of DNA. The aim of this study was to compare neonatal serum folate levels of babies born to smoking and non-smoking mothers.

**Methods** Infants of consenting pregnant mothers presenting at  $\geq 37$  weeks of gestation were enrolled. Subjects were divided into two groups based on their mother's smoking habits. Blood samples were obtained at birth (from the umbilical cord) and 1 month after delivery for the determination of serum folate levels using a chemiluminescence method.

**Results** Among 140 consenting subjects, 108 (77%) brought their newborns to their scheduled visit 1 month after delivery, 68 of whom were non-smokers and 40 were smokers. Babies born to smoking mothers had significantly lower serum folate levels compared to those born to non-smoking mothers, both at birth ( $17.2 \pm 5$  vs.  $24.3 \pm 4.9$ ;  $p < 0.01$ ) and 1 month after delivery ( $11 \pm 4.1$  vs.  $17.5 \pm 4.3$ ;  $p < 0.01$ ).

**Conclusion** Our study is the first of its kind to demonstrate that smoking results in significant reductions in serum folate levels of newborns. These results suggest that folic acid supplementation may be required for expectant smoking mothers throughout pregnancy, not just during the first trimester. Similar supplementation may also be warranted for infants born to such mothers.

**Keywords** Folic acid · Newborn · Smoking

### Introduction

Smoking during pregnancy is associated with an increased risk of maternal and fetal complications [1]. The growth retarding effects of prenatal smoke exposure have been well documented [2], resulting directly in genetic damage in the fetus [3]. It has been postulated that formation of carboxyhemoglobin and nicotine-induced vasoconstriction contribute to fetal hypoxia, which has been implicated in the development of fetal complications [4]. Smoking is associated with decreased maternal levels of folate as well as elevated levels of total homocysteine (tHcy), both of which are in turn associated with adverse pregnancy outcomes [5]. Considering the implications on both maternal and fetal health, the effect of smoking on tHcy and serum folate levels, as modifiable factors associated with poor pregnancy outcomes [6], as well as the potential benefits of folic acid supplementation warrants further investigation.

The aim of this study was to establish the effect of smoking on neonatal serum folate levels, both at birth (cord blood) and 1 month after.

### Subjects and methods

This study was conducted at Zekai Tahir Burak Maternity Teaching Hospital situated in Ankara, with the approval of the local ethics committee. Infants of pregnant women who presented to the outpatient clinic having completed 37 weeks of gestation were enrolled in the study. Mothers were asked to complete a questionnaire on their medical history and smoking status. Those with a history of

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preeclampsia or any acute/chronic illness, as well as those who had previously delivered a small for gestational age infant were excluded.

Samples for serum folate levels were obtained from umbilical cord at birth ( $n = 140$ ) and 1 month after the delivery from infants who applied for follow-up ( $n = 108$ ). The serum was separated immediately and stored at  $-70^{\circ}\text{C}$  until analysis, with all samples analyzed in the same run. Serum folate levels were quantified using the Immulite 2,000 analyzer (Siemens, Llanberis, UK) using a chemiluminescence method.

Infants were divided into two groups based on their mother's smoking habits. Those who had history of smoking at least 10 cigarettes per day were placed in the smokers (SM) group, whereas the remaining patients were considered as non-smokers (NNSM) [7]. Comparisons between the two groups were made using the SPSS, version 15.0 (SPSS Inc. Chicago, IL, USA). 95% confidence intervals (95% CI) were computed parametrically for each reference limit and Student's  $t$  test was used to compare serum folate levels. Chi-square for non-parametric data and Spearman's correlation test for correlations were used. A  $p$  value of  $<0.05$  was considered indicative of statistical significance.

## Results

The demographic characteristics and serum folate levels of study participants are presented in Table 1. A total of 140 expecting mothers consented to participating in the trial during the study period, and 108 (77%) (68 NNSM and 40 SM) of them successfully completed the study by bringing their newborns to the scheduled follow-up visits 1 month after delivery. While the mean serum folate levels of all 140 neonates at birth was  $22.3 \pm 5.9$ , levels were significantly lower in the 108 infants who were tested 1 month after delivery, with a calculated mean serum folate level of  $15.6 \pm 5.1$  ( $p < 0.01$ ). Babies born to smoking mothers had significantly lower levels of serum folate compared to those born to NNSM mothers, both at birth ( $17.2 \pm 5$  vs.  $24.3 \pm 4.9$ ;  $p < 0.01$ ) and at 1 month after delivery ( $11 \pm 4.1$  vs.  $17.5 \pm 4.3$ ;  $p < 0.01$ ) (Table 2). No correlation could be established between use of folic acid supplements during pregnancy and serum folate levels, either at birth ( $r = 0.216$ ,  $p = 0.07$ ) or 1 month after delivery ( $r = 0.156$ ,  $p = 0.08$ ).

## Discussion

The lower serum folate concentrations observed in pregnant women who smoke has important clinical

**Table 1** Maternal and newborn demographic characteristics and serum folate levels of participated infants

Parameters	$n = 140$
Maternal age <sup>a</sup> (years)	$26.6 \pm 5$
Gestational age <sup>a</sup> (weeks)	$38.5 \pm 1.3$
Birth weight <sup>a</sup> (grams)	$3,024 \pm 455$
Male/female ratio of infants	71/69
Cesarean delivery <sup>b</sup>	84 (60%)
Breastfeeding rate <sup>b</sup>	132 (94%)
Maternal smoking <sup>b</sup>	46 (32.8%)
Maternal folic acid supplementation <sup>b</sup>	55 (39.3%)
Duration of folic acid supplementation <sup>c</sup> (months)	2 (1–6)
Mean cord blood serum folate level <sup>a</sup> (ng/mL)	$22.3 \pm 5.9$
Mean one-month serum folate level in offsprings <sup>d</sup> (ng/mL)	$15.6 \pm 5.1$

<sup>a</sup> Values are given as mean  $\pm$  standard deviation

<sup>b</sup> Values are given as percentage

<sup>c</sup> Values are given median and range

<sup>d</sup> Mean level of measured serum folate level of 108 infants 1 month after the delivery

**Table 2** Comparisons between mother-infant pairs in non-smokers (NNSM) and smokers (SM) groups

Parameters	NNSM ( $n = 68$ )	SM ( $n = 40$ )	$p$ value
Maternal age <sup>a</sup> (years)	$26.5 \pm 5.2$	$26.8 \pm 4.4$	NS
Gestational age <sup>a</sup> (weeks)	$38.5 \pm 1.4$	$38.6 \pm 1$	NS
Birth weight <sup>a</sup> (grams)	$2,984 \pm 394$	$3,125 \pm 440$	NS
Breastfeeding rate <sup>b</sup>	65 (95%)	37 (92.5%)	NS
Maternal folic acid supplementation <sup>b</sup>	29 (42%)	18 (45%)	NS
Duration of folic acid supplementation <sup>c</sup> (months)	2 (1–3)	2 (1–6)	NS
Mean cord blood serum folate level <sup>a</sup> (ng/mL)	$24.3 \pm 4.9$	$17.2 \pm 5$	$p < 0.01$
Mean one-month serum folate level in offsprings <sup>a</sup> (ng/mL)	$17.5 \pm 4.3$	$11 \pm 4.1$	$p < 0.01$
Cigarettes per day <sup>a</sup> ( $n$ )	$2.08 \pm 1.09$	$12.2 \pm 2.1$	$p < 0.001$

This kit has no range for infants but serum folate range for adults is 3–17 ng/mL

NS not significant

<sup>a</sup> Values are given as mean  $\pm$  standard deviation

<sup>b</sup> Values are given as percentage

<sup>c</sup> Values are given median and range

implications, as lower levels of serum folate are believed to be responsible for higher rates of miscarriage, stillbirth, abruptio placentae, and fetal anomalies [6, 7]. In a study by Pagan et al. [8] on 196 pregnant women, investigators

observed lower levels of serum folate in SM compared to NONSM both at 18 weeks and at 30 weeks of gestation. They also reported a negative correlation between serum tHcy and serum folate levels. In another study by Relton et al. [9], smoking was found to be associated with significant reductions in maternal but not neonatal erythrocyte folate levels. Similar reductions in the serum folate levels of pregnant smokers have also been reported in another study [10].

Reductions in serum folate levels of smoking pregnant women may be attributed to several factors. Cigarette smoking contributes to oxidative stress and may alter the ability of cells to metabolize and ultimately store folic acid. Furthermore, women who smoke are less likely to adhere to a diet rich in folate or to show compliance to the use of folic acid supplements [11]. However, in a recent study from Canada, no significant difference in dietary folate intake between SM and NONSM was reported [6]. In our study, although we could not evaluate the exact intake related to other dietary and life style factors maternal use of folic acid supplements during pregnancy was not correlated with neonatal serum folate levels.

In a study comparing maternal and neonatal serum folate levels (both at birth and 6 month after delivery) from SM and NONSM mothers, investigators failed to show a statistically significant difference between groups [7]. In another study, while cigarette smoking was found to be associated with lower levels of maternal erythrocyte folate levels, a similar association was not observed with neonatal erythrocyte folate levels [9]. In contrast, we demonstrated lower serum folate levels in offsprings of smoking mothers, both at birth and 1 month after delivery ( $p < 0.01$ ).

We believe that folic acid supplementation should be discussed for infants born to women who smoked during pregnancy and/or continue to smoke after delivery. Folic acid supplements are routinely prescribed to expecting mothers during the first trimester. Being a water-soluble vitamin, folic acid supplementation may be continued throughout pregnancy in smoking mothers to prevent the

development of fetal and neonatal folate deficiency. Lack of reference values is a challenge in pointing out folate deficiency or endangerment of folate deficiency in near future in these infants. However, there is a dire need for more extensive studies to evaluate both the short-term and long-term benefits of maternal and neonatal folic acid supplementation.

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