

Effect of Passive Smoking in Pregnancy on Neonatal Nucleated Red Blood Cells

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ABSTRACT. *Objective.* We evaluated whether the absolute nucleated red blood cell (RBC) count is elevated in term, appropriate for gestational age (AGA) infants born to women exposed to passive smoking in pregnancy.

Patients and Methods. We compared absolute nucleated RBC counts taken during the first 12 hours of life in 2 groups of term, vaginally delivered infants, 1 group born to mothers who were routinely exposed to tobacco smoke during pregnancy ($n = 55$) either at home or at the workplace, and the other to mothers who were not routinely exposed to any tobacco smoke ($n = 31$). We excluded infants of women with conditions known to elevate nucleated RBC counts.

Results. There were no differences between groups in birth weight, maternal age, gravidity, parity, maternal analgesia during labor, 1- and 5-minute Apgar scores. Gestational age was minimally higher in the control group (39.6 ± 1.1 vs $39.2 \pm .8$ weeks). The median absolute nucleated RBC count in the passive smoking group was $357 \times 10^6/L$ (range: $0-5091 \times 10^6/L$) versus $237 \times 10^6/L$ (range: $0-1733 \times 10^6/L$) in nonsmoking controls. Stepwise regression analysis that included Apgar scores, gestational age, and the passive smoking status (yes/no) as independent variables showed significant correlation of absolute nucleated RBC count only with the passive smoking status.

Conclusion. At birth, term AGA infants born to mothers exposed to passive smoking have increased circulating absolute nucleated RBC counts compared with those of controls. We speculate that passive smoking in pregnancy should be avoided, because it may have subtle negative effects on fetal oxygenation. *Pediatrics* 2000; 106(3). URL: <http://www.pediatrics.org/cgi/content/full/106/3/e34>; tobacco, passive smoking, term infants, nucleated red blood cells.

ABBREVIATIONS. RBC, red blood cell; AGA, appropriate for gestational age; WBC, white blood cell; SGA, small for gestational age.

Cigarette smoking during pregnancy is a known risk factor for adverse outcome in the human fetus and infant; there is a warning on cigarette packs by the US Surgeon General against

the effects of smoking during pregnancy. Specifically, maternal smoking significantly increases the risks of spontaneous abortion and of preterm or low birth weight delivery.¹ It is capable of causing fetal growth restriction in the third trimester,² and is associated with increased neonatal morbidity, such as neonatal asphyxia,³ intraventricular hemorrhage,⁴ reduced lung function, and increased incidence of perinatal death³ as well as sudden infant death syndrome.⁵ Maternal cigarette smoking during pregnancy also increases the risk of neurodevelopmental impairment during later childhood.⁶ Although the mechanism of fetal injury seems to involve many factors, it is likely that chronic fetal hypoxia affects the process. We recently demonstrated that a marker of fetal hypoxia, the absolute number of circulating nucleated red blood cells (RBCs), measured at birth, is increased in infants of smoking mothers.⁷ The aim of this study was to demonstrate whether maternal passive exposure to tobacco smoke during the last trimester of pregnancy is also capable of elevating the absolute number of circulating nucleated RBCs measured at birth.

METHODS

We prospectively studied 2 groups of consecutively born term infants (38–41 weeks of gestation by last menstrual period, confirmed by early ultrasound), appropriate for gestational age (AGA) by the intrauterine growth charts of Lubchenco et al,⁸ who were born vaginally at the Lis Maternity Hospital, Tel Aviv Sourasky Medical Center between January 1, 1998 and March 31, 1998. Group 1 consisted of 55 infants of nonsmoking mothers who were exposed to passive smoking in pregnancy (27 at home, 24 at the workplace, and 4 at both locations) and group 2, of 31 infants of nonsmokers, not exposed to passive smoking. The mothers themselves reported being routinely exposed to tobacco smoke during the third trimester of pregnancy. We defined routine exposure as that resulting from a husband (or live-in partner) who smoked at home in the same room(s) on a daily basis, or from exposure at the workplace to other smoking employees, also on a daily basis (except weekends). To control for potential confounders that may be associated with a change in the nucleated RBC count, we excluded infants born to women with gestational or insulin-dependent diabetes⁹; pregnancy-induced hypertension¹⁰; placental abruption or placenta previa¹¹; any maternal heart, kidney, lung, or other chronic condition; drug or alcohol abuse¹²; perinatal infections (eg, fever, leukocytosis, signs of chorioamnionitis)¹³; abnormal electronic intrapartum monitoring¹¹; or infants with low Apgar scores (<8 at 1 or 5 minutes).¹⁴ We also excluded infants with perinatal blood loss or hemolysis (blood group incompatibility with a positive Coombs' test or hematocrit <45%)¹⁵ or chromosomal anomalies.¹⁶

Venous blood samples for complete blood cell counts were collected from the infant within 12 hours of birth and analyzed according to laboratory routine using an STK-S counter (Coulter Corporation, Hialeah, FL). Differential cell counts were performed

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manually and nucleated RBC counts were expressed per 100 white blood cells (WBC). We calculated the number of nucleated RBCs as an absolute number rather than per 100 leukocytes, and the WBC count was expressed as corrected for the presence of nucleated RBCs. Indeed, we showed previously that leukocyte counts and absolute nucleated RBC numbers are dependent.⁹ Thus, traditional expression of nucleated RBCs as their number per 100 WBCs might introduce a significant bias.⁹

Data are reported as mean \pm standard deviation or median (range). Statistical analysis included Kruskal-Wallis test attributable to nonnormal distribution of absolute nucleated RBCs and backward stepwise regression analysis. $P < .05$ was considered significant.

RESULTS

There were no significant differences between groups in terms of birth weight, gender, maternal age, maternal gravidity or parity, epidural analgesia during labor, and 1- and 5-minute Apgar scores (Table 1). However, gestational age in the smoking group was slightly (by <1 week average), but significantly higher than in the control group ($P = .0457$). The absolute nucleated RBC count was significantly higher in the passive smoking group than in the control group. There were no significant differences in WBC counts, platelet counts, RBC counts, hematocrit levels, or lymphocyte counts. Backward stepwise regression analysis using gestational age, Apgar scores, and passive smoking as independent variables, and absolute nucleated RBC counts as the dependent variable was performed. The only variable that remained significantly correlated with the absolute nucleated RBC count was the presence or absence of passive smoking ($R^2 = .06$; $P = .02$).

DISCUSSION

We found that fetal exposure to passive maternal smoking significantly correlates with increased nucleated RBC numbers in term AGA infants. We and others had previously showed that small for gestational age (SGA) and AGA infants of smoking moth-

ers had increased numbers of absolute nucleated RBCs, compared with appropriate controls, in a dose-response relationship.^{8,17} The present study is the first to assess the effects of passive maternal smoking on the neonatal nucleated RBC count. We believe that our study shows that maternal passive smoking is an independent risk factor for increased newborn absolute nucleated RBC counts, because we carefully excluded situations that may influence the nucleated RBC count, such as intrauterine growth restriction,¹⁸ preterm labor with histologic placental signs of chorioamnionitis,¹⁹ hemolysis, chromosomal anomalies, maternal diabetes,^{9,20} and potential neurologic insults.^{21,22} There was a slight difference (<1 week average) in gestational age between the 2 groups; we do not believe this difference affected the results, because the difference in gestational age was minimal, all infants were term, and the effect of gestational age on the nucleated RBC count was insignificant in stepwise regression analysis. Moreover, because nucleated RBC counts decrease with advancing gestational age until term,²³ the difference in gestational age between the 2 groups may have only decreased the significance of the difference in nucleated RBC counts.

We believe that our data, similar to our previous work in smoking mothers,¹⁶ provide evidence that during tobacco smoke exposure in pregnancy, the absence of growth restriction should not be interpreted as evidence of normal fetal oxygenation. Similarly, Varvarigou et al²⁴ found increased cord blood erythropoietin concentrations in AGA infants born to smoking mothers. Although increased erythropoietin was not seen in all infants born to smoking mothers, the authors concluded that "1 of 5 fetuses who are exposed to tobacco smoke are in a state of chronic hypoxia."²⁴

The mechanism by which maternal smoking increases circulating neonatal absolute nucleated RBC counts is unknown. A likely explanation is relative fetal hypoxia, but the mechanisms that may be involved are multiple. In theory, there may be nicotine-induced placental vasoconstriction,²⁵ decreased fetal tissue oxygenation attributable to production of fetal carboxyhemoglobin, and placental vascular disease.²⁶ Other indicators of fetal hypoxia during maternal smoking include fetal growth restriction,² increased risk of spontaneous abortion,¹ and neurodevelopmental anomalies¹ that occur more frequently among infants of smoking mothers.

In this study as in our previous one, the mean hematocrit of infants of smoking mothers did not differ significantly from that of nonsmokers. We had speculated that it might be attributable to the fact that we had excluded infants who might have been exposed to the most severe hypoxia, such as SGA infants, those born after abnormal electronic intrapartum monitoring, and those with low Apgar scores. In those more severe cases, prolonged or significant hypoxia might sufficiently stimulate bone marrow to cause a rise in hematocrit. Alternatively, one could postulate that exposure to cigarette smoke might increase turnover in utero. We must recognize some potential limitations of our study. First, be-

TABLE 1. Demographic and Hematologic Characteristics†

Characteristic	Controls <i>n</i> = 31	Passive Smokers <i>n</i> = 55
Birth weight (g)	3347 \pm 508	3400 \pm 393
Gestational age (wk)	39.1 \pm .8	39.6 \pm 1.1*
Gender (males:females)	14:17	28:27
Maternal age (y)	30.2 \pm 5.0	28.9 \pm 4.9
Gravidity	2.2 \pm 1.3	2.2 \pm 1.6
Parity	1.7 \pm .9	2.0 \pm .9
Epidural analgesia during labor	22 (71)	46 (84)
1-min Apgar score	9 (9-10)	9 (8-10)
5-min Apgar score	10 (9-10)	10 (9-10)
Hematocrit	.64 \pm .07	.65 \pm .08
RBCs ($\times 10^9/L$)	30.4 \pm .6	30.0 \pm .8
White blood cells (corrected) ($\times 10^9/L$)	19.8 \pm 7.4	19.8 \pm 6.0
Platelets ($\times 10^9/L$)	244 \pm 70	267 \pm 67
Absolute lymphocyte count ($\times 10^9/L$)	6.7 \pm 1.6	6.8 \pm 8.5
Absolute nucleated RBCs $\times 10^6/L$	237 (0-1700)	357 (0-5100)**

* $P = .046$.

** $P = .02$. No other differences were statistically significant.

† All data expressed as mean \pm 1 standard deviation or *n* (percent), except Apgar scores and absolute nucleated RBCs, which are expressed as median (range).

cause smoking exposure history was obtained only from the mother of each infant, we cannot rule out some underreporting of smoking habits. We did not perform measurements of cotinine,²⁷ a biological marker of smoking, because we were only interested in long-term passive exposure to tobacco smoke. Based on our previous study of infants of smoking mothers, there was a correlation between number of cigarettes smoked and the nucleated RBC counts.⁷ If we make the assumption that passive smoking affects nucleated RBC in a manner similar to active smoking, then the average fetus was exposed through his mother to the equivalent of ~6 cigarettes per day.⁷ A second limitation of our study is that we cannot exclude the possibility that some infants in the control group were exposed to nicotine or to other sources of tobacco smoke or carbon monoxide. Despite these limitations, the absolute nucleated RBC count of infants exposed to maternal passive smoking was significantly higher than that of nonexposed controls. We believe that our data give further support for health care providers to counsel mothers to not expose themselves to passive smoking in pregnancy and to insist on strict enforcement of smoking regulations at the workplace.

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