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The Influence of Prenatal Exposure to Tobacco Smoke on Neonatal Body Proportions

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Abstract

The objective of this study was to determine neonatal anthropometric indices such as: birth weight, crown-heel length, head and chest circumference and ponderal index, in relation to the maternal smoker status (active and passive smoking). The study included 147 neonates born in 2003-2004 at the Princess Anna Mazowiecka University Hospital in Warsaw admitted to the Neonatal and Intensive Care Department of Warsaw Medical University. Neonates were assigned to one of three groups: babies of mothers who were active smokers, passive smokers and non-smokers based on a questionnaire concerning exposure to tobacco smoke and on the concentration of cotinine in maternal urine. The babies of mothers who were active smokers were born with lower birth weight (p=0.033), lower crown-heel length (p=0.026), lower head circumference (p=0.002) and lower chest circumference (p=0.021) significantly more often than babies of non-smoker mothers. Babies whose mothers were active smokers had an increased risk of lower head circumference or 3, 9 (1, 4-10, 7, CI 95%), and an increased risk of lower chest circumference OR 4, 0 (1, 5-10, 9, CI 95%). The babies of mothers who were passive smokers also had lower anthropometric indices, but the differences were not statistically significant. No effect on ponderal index was observed among the neonates whose mothers were active and passive smokers. Smoking during pregnancy causes symmetrical restriction of intrauterine growth.

Keywords: Neonate; Active smoking; Passive smoking; Cotinine; Birth weight; Crown-heel length; Head circumference; Chest circumference; Ponderal index

Introduction

Tobacco smoke has a harmful influence on the development of the fetus not only when the mother is an active smoker, but also when a pregnant woman is exposed to tobacco smoke in the environment (passive smoking). Of over 4200 constituents of tobacco smoke, the most harmful to the fetus are: nicotine, carbon monoxide, nitrogen oxide, hydrogen cyanide, cadmium and reactive forms of oxygen. The direct influence of nicotine, changes in placental structure, formation of pathological hemoglobin (carboxyhemoglobin, methemoglobin, cyanmethemoglobin) result in persistent hypoxia of fetal tissue and a decreased supply of nutrients. Babies of mothers who are smokers have a birth weight of 154–459 g lower than those of non-smoker mothers and the deficit in birth weight increases proportionally to the number of cigarettes smoked by the mother [1-8]. Some authors confirm that the association between maternal cigarette smoking during pregnancy and reduced birth weight is modified by maternal genetic susceptibility. They suggest an interaction between metabolic genes and cigarette smoking [4,5]. Smoking during pregnancy impairs not only weight gain, but also growth of body length, head and chest circumference [1-8]. The objective of this study was to determine neonatal anthropometric indices such as: birth weight, crown-heel length, head and chest circumference and ponderal index, in relation to maternal smoker status (passive and active smoking).

Material and Methods

The study included 147 neonates born in 2003-2004 at the Princess Anna Mazowiecka University Hospital in Warsaw and admitted to the Neonatal and Intensive Care Department, Medical University of Warsaw. Live-born neonates from singleton pregnancies, whose mothers gave informed consent and completed a questionnaire which assessed the level of tobacco smoke exposure during pregnancy, were included in the study. The study protocol was approved by the Bioethical Committee of Warsaw Medical University. Investigations were conducted in accordance with the 1975 Helsinki Declaration. The subjects were divided into three groups based upon the questionnaire regarding exposure to tobacco smoke and on the concentration of cotinine in maternal urine. There were 58 subjects whose mothers were active smokers; the mothers declared themselves as such and their urine cotinine level was >200 ng/mg creatinine. Subjects whose mothers were passive smokers exposed to environmental tobacco smoke during pregnancy numbered 64 (cotinine level in maternal urine ranged from 5-200 ng/mg creatinine). The number of subjects whose mothers were non-smokers and had no environmental exposure was 25 (the maternal urinary cotinine level was <5 ng/mg creatinine). Some mothers underestimated the degree of tobacco smoke exposure during pregnancy and this was corrected by an assessment of cotinine levels in the urine. 5 neonates whose mothers declared passive smoking in the questionnaire and 7 neonates of women who declared no exposure to tobacco smoke were included in the group of neonates whose mothers were active smokers, because the level of cotinine in the mother's urine was >200 ng/mg creatinine. A further 19 babies of women with urine cotinine levels in the 5-200 ng/mg creatinine range were included in the passive smoker group, although their mothers had denied exposure to tobacco smoke in the questionnaire.

In the first 24 hours after delivery a 5ml urine sample was collected

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from the mother. The sample was frozen at a temperature -80°C and stored until cotinine levels were established. The level of cotinine was quantified by High Performance Liquid Chromatography (HPLC). The urinary concentration of cotinine was standardized by comparison with creatinine excretion and the results were expressed as the cotinine: creatinine ratio (ng/mg).The gestational age of newborns in the study was between 26 and 42 weeks and the average gestational age were 38 weeks. The majority of subjects - 114 (77.6%) were delivered at term, the remaining 33 (22.4%) were premature. There was no statistically significant difference in gender, mode of delivery, number of preterm newborns between the 3 groups of subjects (Table 1). Directly after delivery anthropometric indices were recorded: birth weight (g), crown-heel length (cm) and head and chest circumference (cm). Birth weight was determined with electronic scales with up to 10 g accuracy. Crown-heel length, head and chest circumference were measured with tape measure with up to 0.5 cm accuracy. Head circumference was recorded above the orbita, chest at the level of the nipples. The ponderal index was defined as 100 x [birth weight (g)/crown – heel length (cm)^3]. The Statistical Analysis System (SAS) program package was used for statistical analysis. Descriptive statistics were calculated for each parameter. The Shapiro-Wilk test was used to verify the hypothesis concerning the correspondence of the distribution of quantitative variables with the normal distribution. The Kruskal-Wallis test was used to compare the groups for quantitative variables with a distribution different from normal. Differences between the two groups for quantitative variables with a distribution different from normal were tested using Wilcoxon test. Fisher′s exact test was used in the analysis of the relationships between qualitative variables. The associations between anthropometric indices and maternal smoker status and other confounding factors such as: gender, gestational age and complications of pregnancy were assessed using the multivariate logistic model (GLIMMIX). In order to make the analysis more credible, the variables were discretized into four levels in accordance with the quartiles and cumulative logit model for ordered response was used. The odds ratio was calculated. P-values less than 0.05 were considered statistically significant.

Results

The lowest birth weight was observed in subjects whose mothers were active smokers and the difference between the birth weight of subjects whose mothers did not smoke was statistically significant p = 0.033. The median birth weight in this group of subjects was 3175 g and it was 230 g lower than the birth weight of subjects whose mothers were passive smokers and 325 g lower than the birth weight of subjects whose mothers were non-smokers. Median birth weight in the group of subjects with passive tobacco exposure during pregnancy was 3405 g and it was 95 g lower than the birth weight of subjects with no tobacco exposure during pregnancy. However, the difference was not statistically significant (Table 2). Median crown-heel length of the subjects with active tobacco exposure was 53 cm and it was 1 cm shorter than the median crown-heel length of the subjects with no tobacco exposure during pregnancy. The difference was statistically significant (p=0.026) (Table 2). The lowest values for head circumference were noted in the group of subjects with active tobacco exposure during pregnancy. In this group the median head circumference was 33 cm and it was 1 cm lower than in the group of subjects with passive tobacco exposure (34 cm) and 2 cm lower than in those with no tobacco exposure during pregnancy (35 cm). The difference between head circumference of subjects with tobacco exposure and no tobacco exposure during pregnancy was statistically significant (p=0.002). The median head circumference of subjects with passive tobacco exposure was also 1 cm lower than no tobacco exposure during pregnancy, but the difference was not statistically significant (Table 2). Subjects whose mothers smoked cigarettes during pregnancy also had a lower chest circumference than those whose mothers were passive smokers and non-smokers. Median chest circumference in the group of subjects whose mothers were active smokers was 32 cm. The difference was statistically significant (p=0.021) in comparison with the group of subjects whose mothers were non-smokers (Table 2). The median ponderal index in all three groups of subjects was similar and it was respectively: 2.11 (babies of active smokers), 2.09 (babies of passive smokers), 2.14 (babies of non-smokers) (Table 2). Logistic regression models to estimate the association of maternal cigarette smoking with anthropometric indices in relation to other confounding factors such as: gender, gestational age and complications of pregnancy showed that active smoking by pregnant women has a statistically significant influence on the head and chest circumference of neonates. The babies with active tobacco exposure were at 3.9 (1.4-10.7, CI 95%) times greater risk of reaching lower head circumference, 4.0 (1.5-10.9, CI 95%) times greater risk of reaching lower chest circumference compared with those with no tobacco exposure during pregnancy. In the group of subjects whose mothers were active smokers throughout pregnancy there was also a tendency towards lower birth weight 2.6 (1.0–6.9, CI 95%) and lower crown-heel length 2.4 (0.9–6.6, CI 95%). The odds ratio value was close to statistical significance. In the case of neonates of mothers who were exposed to tobacco smoke during pregnancy (passive smokers) the risk of lower birth weight and crown-heel length as well as head and chest circumference was also higher, but this was not statistically significant (Table 3).

Discussion

Many authors report that smoking during pregnancy has a negative influence on growth of the fetus. They often use a questionnaire to assess maternal smoking status. But the smoking habit reported by mothers themselves is not an accurate measure of fetal tobacco exposure, particularly with regard to passive smoking [9]. In our study some mothers underestimated the degree of tobacco smoke exposure during pregnancy. Therefore the smoking status of the mothers was corrected by an assessment of cotinine levels in the mother′s urine. The results of our study were similar to others which confirmed that neonates with tobacco exposure during pregnancy have lower birth weight, crown-heel length, head and chest circumference [1-15]. In our study the difference in birth weight between neonates with and without tobacco exposure during pregnancy was 325g (p=0.033). Similarly, neonates whose mothers were passive smokers, hence less exposed to tobacco

Characteristic	Neonates with active smoker mothers n=58	Neonates with passive smoker mothers n=64	Neonates with non-smoker mothers n=25	P value
Sex Male Female	 32 (55.2%) 26 (44.8%)	 38 (59.4%) 26 (40.6%)	 15 (60.0%) 10 (40.0%)	n.s.
Gestational age ≥ 37 weeks <37 weeks	 42 (72.4%) 16(27.6%)	 52 (81.3%) 12(18.7%)	 20(80.0%) 5(20.0%)	n.s.
Delivery spontaneous labor vacuum extractor cesarean section	 32(55.2%) 1 (1.7%) 25(43.1%)	 35(54.7%) 0 (0.0%) 29(45.3%)	 12(48.0%) 1 (4.0%) 12(48.0%)	n.s.

p value against newborns of non-smoking mothers
n.s. - not statistically significant

Table 1: Characteristics of the neonates.

Variable	Median	Minimal value	Maximal value	Mean ± SD	P value
Birth weigh (g)					
NN n=25	3500	2330	5140	3482 ± 715	
NP n=64	3405	1170	5200	3289 ± 765	n.s.*
NA n=58	3175	990	4860	2976 ± 858	p=0.033*
Crown-heel length (cm)					
NN n=25	54	48	63	54 ± 4	
NP n=64	54	39	63	53 ± 4	n.s.*
NA n=58	53	34	59	51 ± 6	p=0.026*
Head circumference (cm)					
NN n=25	35	32	38	34 ± 2	
NP n=64	34	27	37	34 ± 2	n.s.*
NA n=58	33	25	38	33 ± 2	p=0.002*
Chest circumference (cm)					
NN n=25	33	27	40	33 ± 3	
NP n=64	33	22	38	33 ± 3	n.s.*
NA n=58	32	22	40	31 ± 4	p=0.021*
Ponderal index					
NN n=25	2.14	1.68	2.53	2.14 ± 0.22	
NP n=64	2.09	1.31	2.67	2.12 ± 0.22	n.s.*
NA n=58	2.11	1.61	2.80	2.14 ± 0.28	n.s.*

* p value against NN
n.s.-not statistically significant
NN-neonates with non-smoker mothers
NP-neonates with passive smoker mothers
NA-newborns with active smoker mothers

Table 2: Median of birth weight, crown-heel length, head circumference, chest circumference and ponderal index value.

Independent variable	Birth weight OR (95% CI)	Crown-heel length OR (95% CI)	Head circumference OR (95% CI)	Chest circumference OR (95% CI)	Ponderal index OR (95% CI)
Active smoker vs. non-smoker	2.6 (1.0–6.9)	2.4 (0.9–6.6)	3.9 (1.4–10.7) *	4.0 (1.5–10.9) *	1.1 (0.43–2.64)
Passive smoker vs. non-smoker	1.5 (0.6–3.7)	1.3 (0.5–3.5)	1.9 (0.7–5.2)	1.4 (0.5–3.4)	1.2 (0.5–2.8)
Complications of pregnancy No / Yes	0.9 (0.5–1.9)	0.8 (0.4–1.5)	1.5 (0.8–3.0)	1.3 (0.6–2.5)	1.1 (0.6–2.0)
Newborn sex male / female	0.5 (0.3–1.0)	0.4 (0.2–0.8) *	0.5 (0.2–0.9) *	0.6 (0.3–1.2)	1.2 (0.6–2.2)
Gestational age <37 weeks / ≥ 37 weeks	60.7 (19.5-188.6) *	118.8 (31.8-443.3) *	21.8 (8.2–57.8) *	59.8 (19.3-185.0) *	1.8 (0.8–3.7)

*p-value < 0.05-*p-value < 0.05-significant differences

Table 3: Odds ratio (OR) [95% confidence interval - CI] for birth weight, crown-heel length, head and chest circumference, ponderal index according to the smoker status of the mother, complications of pregnancy, sex and gestational age of the neonate.

smoke in fetal life, achieved a 30-53 g lower birth weight [2-12]. In our study neonates of mothers who were passive smokers achieved a 95 g lower birth weight and 1 cm lower head circumference than neonates of mothers who did not smoke, but the differences were not statistically significant. Multivariate logistic model assessing relationships between anthropometric indices and maternal cigarette smoking status, gender, gestational age and complications of pregnancy showed that in the group of neonates whose mothers were active smokers there was a higher risk of lower head circumference 3.9 (1.4-10.7, CI 95%) and lower chest circumference 4.0 (1.5-10.9, CI 95%). The odds ratios for lower birth weight 2.6 (1.0-6.9, CI 95%) and lower crown-heel length 2.4 (0.9-6.6, CI 95%) were close to statistical significance. As reported by Roquer et al. exposing a pregnant woman to cigarette smoke had a similar effect on the anthropometric parameters of neonates (birth weight, crown-heel length and head and chest circumference) as smoking<10 cigarettes a day. The study showed a reduction in body length in the babies of passive smoker mothers by 1 cm compared with those of mothers who did not smoke [13]. The difference in crown-heel length between neonates with and without tobacco exposure during pregnancy ranges, according to different authors, from 0.79-2.3 cm [2-8]. In our study this difference was 1cm (p=0.026). Lindley et al. showed that reduction in crown-heel length is associated with the number of cigarettes smoked by the mother. Crown-heel length deficit in babies whose mothers smoked less than 10 cigarettes a day during pregnancy, was lower in comparison with those whose mother did not smoke (0.62 cm) and those whose mothers smoked over 10 cigarettes a day (crown-heel length deficit was 0.89 cm). A statistically significant deficit in crown-heel length was also observed in babies whose mothers had stopped smoking from the 32 week of pregnancy. This fact provides evidence for the negative and irreversible influence, already in early pregnancy, of tobacco smoke on body length increase [6]. Jaddoe et al. registered the weekly lower increase in femoral bone length by 0.19 mm (-0.23-0.14, CI 95%), statistically more often, in fetuses of mothers who smoked ≥ 9 cigarettes/day. Lower fetal growth parameters were registered in the sonogram from the 10th week of gestation. The same authors also showed a significantly lower increase in head circumference by 0.56 mm (-0.73-0.40, CI 95%) from the 25th week of gestation [7]. Ponderal index calculated to establish neonatal body proportions reflects the relationship between body weight and length is independent of race or gender. It increases with gestational age, because with maturation the weight of the body increases more than its length. In children with growth retardation, a normal ponderal index will indicate a proportional reduction in weight and length (symmetric growth retardation), whereas a low ponderal index may

suggest that weight is more affected than length (asymmetric growth retardation). In our study comparable values of ponderal index in both groups: babies with active tobacco exposure (2.11) and of without tobacco exposure during pregnancy (2.14) prove that smoking tobacco by the mother inhibits the increase of both the weight and the length of the body. Neonates with tobacco exposure during pregnancy tend to be symmetrical in their growth retardation. Other authors also observed no significant effect of smoking in the prenatal period on the ponderal index. Values of the ponderal index were comparable between the group of neonates whose mothers smoked and those whose mothers did not smoke during pregnancy [8,14]. Lindley *et al.* proved that continued smoking throughout pregnancy was associated with an increase in ponderal index. Infants of smokers tend to be shorter and have a higher ponderal index, while the infants of non-smokers tend to be longer and have a lower ponderal index. Infants of smokers who stopped smoking also had a statistically significant increase in ponderal index of 0.027 (95% CI, 0.009, 0.045) compared with the infants of nonsmokers of the same birth weight and gestational age [6]. The main reason of fetal growth disorders in mother with tobacco exposure during pregnancy is decreased supply of nutrients and of oxygen during fetal life. The factors accounting for this condition are: morphological changes in the placenta of smoker mothers and limitation of blood flow in the intervillous space of the placenta associated with the direct vasoconstrictor effect of nicotine [1,15]. Furthermore, nicotine inhibiting the active transport of amino acids in the placental microvilli decreases protein synthesis by the fetus and due to decreased serum concentrations of the fetal growth hormones (insulin, IGF-I and its binding protein IGFBP-3) [1,16]. Nicotine penetrates directly into the fetal circulation. The presence in placental tissue of cytochrome CYP2A6, whose enzymes participate in biotransformation of nicotine into cotinine, was not confirmed. Therefore, the human placenta does not pose a metabolic barrier to nicotine transfer to the developing fetus [1]. The extent of birth weight deficit in neonates with mothers who smoked during pregnancy is associated with the genetically determined ability to biotransform nicotine. Wang et al. showed the difference in body weight reduction in neonates with active tobacco exposure during pregnancy mothers depending on the arrangement of alleles in the genes coding for enzymes participating in nicotine biotransformation. In those cases when the arrangement of alleles in maternal genotype for the gene CYP1A1 was AA, reduction of neonatal birth weight of smoker vs. non-smoker mothers was 252 g. However, if the arrangement of alleles for this gene was Aa or aa, the birth weight of neonates with mothers who were active smokers was 520 g lower. The presence of gene GSTT1 caused the decrease of birth weight by 285 g, while its absence caused the reduction of birth weight by 642 g. The greatest birth weight reduction took place with the allele's arrangement Aa/aa for gene CYP1A1 and simultaneous absence of gene GSTT1 [4]. Restricted fetal growth is therefore the result not only of adverse influence of tobacco smoke, but also of the negative interaction between metabolic genes and cigarette smoking.

Conclusions

1. Neonates with mothers who actively smoked during pregnancy have statistically significantly lower birth weight, crown-heel length, head and chest circumference than neonates with mothers who did not smoke and were not exposed to tobacco smoke during pregnancy.
2. Ponderal index determining body proportions is comparable in the case of neonates whose mothers were active smokers and those who were non-smokers during pregnancy.
3. Smoking during pregnancy causes symmetrical restriction of intrauterine growth.

Study limitations:

The non-homogeneity of the neonatal subjects was a study limitation. The subjects included 22.4% of neonates who were born prematurely between 26–37 weeks of gestation. This had an impact on the results of anthropomorphic measurements, although the difference in the frequency of prematurity in the study groups was not statistically significant and therefore the groups were comparable with one another.

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