PRENATAL EXPOSURE TO ENVIRONMENTAL XENOBIOTICS AND ALLERGY DEVELOPMENT IN CHILDREN

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SUMMARY: Prenatal factors seem to play important role in determining susceptibility to atopy and asthma. Maternal exposure to environmental xenobiotics during pregnancy represents potential exposure of the foetus via placental transfer. Environmental xenobiotics may adversely affect intrauterine life quality and development of foetal immune system. International project „Epidemic investigation of allergic diseases among children in the SR" focused on the relationship between selected environmental factors (including xenobiotics) and allergy (AD) development in children, has been launched in 1997 in Slovakia. In 8 environmentally different Slovak regions mothers with newborns were recruited. In randomly selected mothers, set of biological samples was collected at delivery: placental samples for chemical analyses (concentrations of selected organochlorine compounds and toxic metals) and histopathological analyses, and umbilical blood samples for the measurements of total IgE (uIgE) concentrations. Significant differences were found in the xenobiotic concentrations in the placental samples among regions. Placental concentrations of cadmium (Cd) and lead (Pb) positively correlated with the frequency of pathological lesions in the placental tissue. The most important predictor of uIgE positivity was living in agricultural region. Placental Cd concentration was in negative correlation with total uIgE ($r=-0.2$; $p<0.001$). The incidence of AD was 12% in 12-month-old children; the most frequent allergic diagnosis was atopic eczema (7.7%). The placental total sum of organochlorine compounds was significantly higher in the group of children with diagnosed atopic eczema ($p<0.05$). Higher placental Pb concentration was associated with higher frequency of asthma respiratory symptoms (ARS) in children ($p<0.05$). The results support the hypothesis that timing of the environmental exposure is of importance for the immune system with respect to allergy development.

INTRODUCTION: There has been a significant increase in the prevalence of allergic symptoms in children and young adults, mainly in industrialised countries (1). Since it seems unlikely that genetic factors would contribute to this rising trend, environmental factors are supposed to play an important part in the development of allergies (AD).

Recent research has demonstrated that events taking place during the gestational period may well play a role in determining whether or not a genetic susceptibility becomes translated into disease processes (2, 3). Human placenta provides the interface between mother and foetus and helps to maintain homeostasis for developing foetus. Thus placental quality represents a major factor affecting the quality of intrauterine life. There is increasing evidence that an altered *in utero* environment may impair foetal development and physiological function, increasing susceptibility to disease in later life (4).

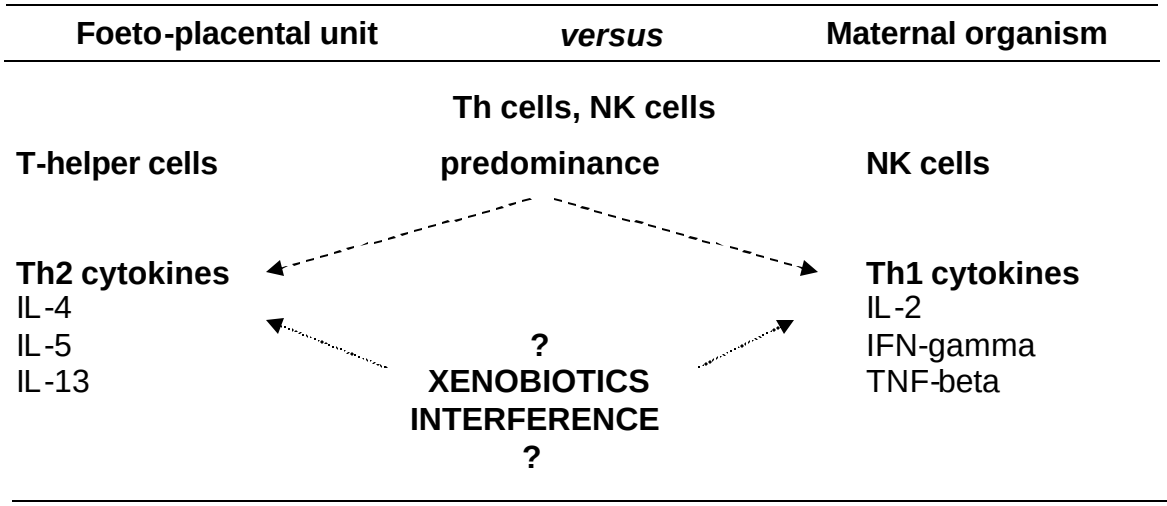
Maternal exposure to xenobiotics during pregnancy, or in time preceding the conception, may have an important impact on the quality of intrauterine life and foetal development, since human placenta does not form the real barrier for the transport of environmental xenobiotics. Some xenobiotics are transported readily through the placenta and some are partially accumulated in the placental tissue, and only partially transferred via placenta to the foetus (e.g. heavy metals). Our previous results on the contamination of human term-placentas with

organic and inorganic xenobiotics in selected Slovak regions have shown a broad spectrum of environmental chemicals captured in the term-placentas (5,6). Using histochemical methods, we found that the main place for the placental heavy metal accumulation was the surface layer of the placental chorionic villi representing the major site for materno-foetal exchange (7).

Persistent organochlorine pollutants (POPs), as lipophilic substances, are easily transported across the placenta. Differences in the placental concentrations of organochlorine compounds among environmentally diverse Slovak regions reflected predominant type of anthropogenic activity in the region (6, 8). Polish authors have found high frequency of immature placental tissue, and disturbed vascularisation and enzyme activity of the placental villi in the regions polluted by industry. As the result of tissue adaptation to hypoxia, "emergency villi" were created, but their efficacy for materno-foetal transport of nutrition was low. Subsequently, foetal hypoxia and low birth weight occurred (9, 10).

Foetal-placental immune system helps to maintain successful pregnancy. We hypothesised that xenobiotics may interfere with these immune processes and contribute to susceptibility to allergy (Figure 1). The main aim of our study was to assess the association between the environmental quality of intrauterine life and AD development in early childhood.

Figure 1*: Cellular immune system during pregnancy*



METHODS: The US-Slovak project "Epidemic Investigation of Allergic Diseases among Children in the Slovak Republic, 1996-2000" focused on the relationship between environmental factors (including intrauterine life quality) and AD development in children, was launched in 1997. The cohort study was based on 1978 full-term deliveries. Mothers with newborns were recruited at regional maternity hospitals according to enrolment criteria in 8 Slovak regions selected by different environmental characteristics (regions polluted by mining/metallurgy, chemical industry, agricultural regions and rural region as relatively less polluted area). In randomly selected mothers (N=360), placental samples for histological and chemical analyses (selected organochlorine compounds and toxic metals lead-Pb and cadmium-Cd) and umbilical cord blood samples for determination of total immunoglobulin E (uIgE) were collected. Placental samples for histological analyses were fixed in buffered formaline, stained by haematoxylin-eosin and examined by light microscope. Concentrations of Pb and Cd in the placental tissue were assessed using atomic absorption spectrometry (5) and the concentrations of organochlorine compounds (selected chlorinated benzenes,

organochlorine insecticides and polychlorinated biphenyls - PCBs) were determined by capillary gas chromatography (6). Total uIgE was determined by fluoroimmunoassay (Pharmacia CAP System RAST® FEIA). Regional allergists examined 12-month-old children for allergy manifestation and questionnaires focused on prenatal and postnatal environmental risk factors for allergy development were filled. Statistical evaluation was performed using statistical softwares EpiInfo and STATA 6.0.

RESULTS AND DISCUSSION: Comparing the placental Pb and Cd concentrations among regions, only small differences were found, supporting the idea of ubiquitous presence of both toxic metals in the environment. Higher placental Pb concentrations were found in the regions polluted mainly by metallurgy and agricultural activity if compared to others. Smoking mothers had significantly higher Pb concentration in the placentas if compared to non-smoking ones ($p= 0.001$). In contrast, the higher placental concentration of Cd was determined in chemical regions and in the rural region. There was no difference in placental Cd concentrations comparing smokers and non-smokers.

The highest contents of total sum of analysed organochlorine compounds were found in the region characterised by PCBs production in the past. Although the production of PCBs was stopped in late 80-ies, their residues are still present in the environment.

Both, placental Pb and Cd concentrations were in a positive correlation with the frequency of placental microstructural lesions (Table 1). These results pointed to the adverse impact of toxic metals on placental quality resulting in higher frequency of microstructural lesions. Deposition of metal particulates in the syncytiotrophoblast of placental chorionic villi may evoke hypoxia and subsequent adaptive structural changes (e.g. ischemic proliferation of syncytiotrophoblast). Since the chorionic villous tree is responsible for crucial functions related to the physiological foetal development, its metal particulate burden may adversely influence important prenatal/postnatal processes.

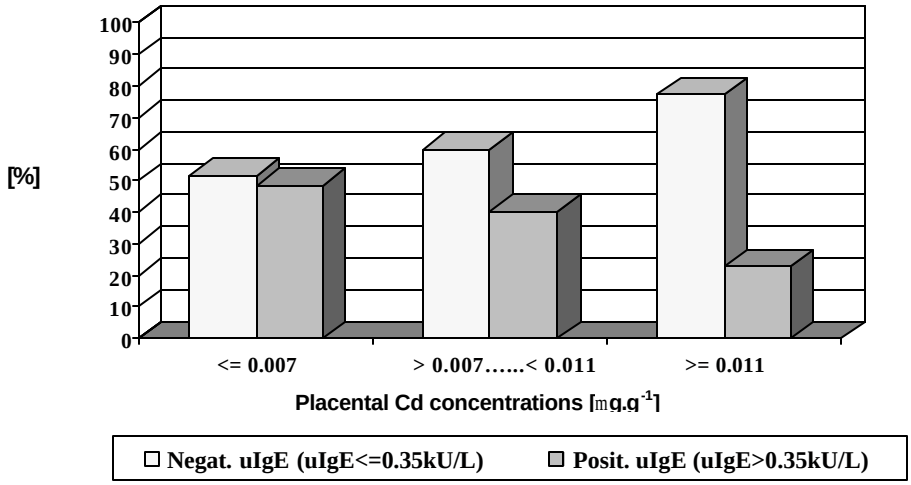
Table1. *Correlation between placental microstructural lesions and Pb and Cd concentrations*

Microstructural lesion	*Compound*	*Relationship*	
Total sum of lesions	Cd	r = 0.11	p<0.05
Ischemic proliferation of syncytiotrophoblast	Pb	r = 0.12	p=0.02
	Cd	r = 0.14	p=0.007
Calcification	Pb	r = 0.21	p<0.001

Prevalence of total uIgE positivity (> 0.35 kU/L) in the total cohort was 37.2% and it was associated with living in agricultural region and the mother's self-reporting ADs (OR=3.2, CI: 1.9-5.4; and OR=1.8, CI: 1.2-2.9, respectively). Significant negative correlation was found between placental Cd concentrations and levels of uIgE ($p<0.001$, $r = -0.2$; Figure 2). Cadmium is known to have immune modulating effects. Increased body burdens of Cd in school children in heavily polluted regions of eastern Germany were associated consistently with dose-dependent suppression of immediate hypersensitivity (11). *In vitro* trials on human B lymphocytes showed that Cd inhibited selectively synthesis of IgE, not of other immunoglobulins (12).

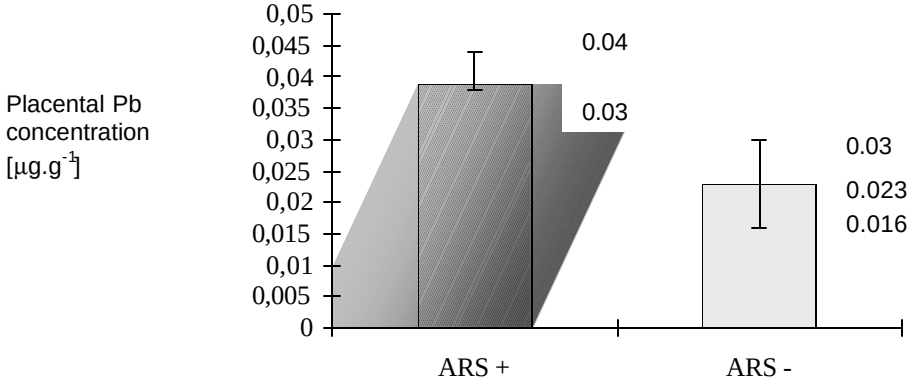
Positive correlation was found between the uIgE levels and placental contents of 1,2-DCB ($r = 0.25$; $p < 0.01$). In our Pilot Project, also the significant correlations between p,p´-DDE as well as PCB 118 placental concentrations and uIgE levels were found ($r = 0.33$, $p= 0.01$; $r = 0,35$, $p<0,01$, respectively) (8). DDE has been identified as a substantial risk factor for asthma and for increased IgE blood levels in children (13).

Figure 2: *Placental Cd concentration (25%ile, median, 75%ile) and uIgE positivity*



The prevalence of diagnosed AD among 12-month-old children was 12%, with the highest AD prevalence in agricultural regions. The prevalence of asthma respiratory symptoms (ARS) was significantly associated with higher placental Pb concentration ($p< 0.05$, Figure 3). Additionally, ARS were found to be more frequent among infants whose mothers smoked before pregnancy (25% vs. 11%, $p<0.05$). Asthma respiratory symptoms occur often among children in early childhood and may indicate asthma development later in life. After adjustment for smoking, the relationship between placental Pb concentrations and ARS remained significant (aOR= 2.61, 95% CI: 1.19, 5.69). It is suggested that Pb exposure *in utero*, or during lactation might increase risk for atopy in children (14).

Figure 3. *Relationship between placental Pb concentrations (25%ile, median, 75%ile) and ARS prevalence in infants at 12-months of age*



The most frequent allergic diagnosis among infants was atopic eczema (7.7%). Total placental contents of organochlorine compounds were significantly higher in children with atopic eczema (medians [$\mu g.g^{-1}$]: 0.011 vs. 0.006; $p<0.05$).

CONCLUSIONS: Contamination of human placenta represents unique biomarker of environmental exposure of women (and a good proxy measure for the foetal exposure). *In utero* exposure to low levels of environmental xenobiotics may result in functional changes in tissues leading to increased susceptibility to disease later in life, including allergy

development/manifestation. Obtained results underline the risk of environmental exposure within pregnancy period with respect to allergy development.

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