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Fetal Stress, Inflammatory Marker and Childhood Asthma

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Abstract

Background: Asthma research has focused on postnatal exposures, but there is recent evidence to indicate immune responses might be initiated in fetal period. Systemic Inflammatory processes during pregnancy might affect fetal lung development that could increase propensity in the child to develop lung diseases.

Objective: To identify the association of C-reactive protein (CRP) levels in Pregnant (with stress in second trimester), newborn blood samples (cord blood) with childhood wheezing.

Methods: Serum CRP concentrations (Turbidimetric method) were measured in maternal blood on the 13-17 weeks of gestation in 32 pregnant women and in the newborn cord blood after delivery. During1 year the frequency of wheezing diseases evaluated by the International Study on Asthma and Allergy in Childhood (ISAAC). Results: Maternal C-reactive protein was associated with the wheezing and lower respiratory tract infections r=.413*; - p=0.019. Compared to children with cord blood C-reactive protein high level had increased risks of wheezing, r=572; p=0.001

Conclusion: Our results suggest that elevated maternal and Cord blood CRP levels are associated with wheezing and lower respiratory tract infections in the first years and predictive asthma young in life.

Keywords: Fetal stress; CRP; Childhood asthma.

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1. Introduction

Asthma research has focused on postnatal exposures, but there is recent evidence to indicate immune responses might be initiated in fetal period. Systemic Inflammatory processes during pregnancy might affect fetal lung development that could increase propensity in the child to develop lung diseases

C-reactive protein is an acute phase protein that increases in response to infectious and non-infectious stimuli, and is generally used as a marker for systemic inflammation [1]. Studies have shown that elevated C-reactive protein levels are associated with a reduced lung function, COPD, and asthma in adults [2-4] and children [5. Elevated maternal C-reactive protein levels during pregnancy lead to fetal growth restriction6, and are associated with endothelial dysfunction, vascular dysfunction and suboptimal placental development [7-9]. These findings suggest that inflammatory processes in the mother during pregnancy lead to fetal developmental adaptations and a greater susceptibility of impaired respiratory health in childhood. Elevated levels of maternal C-reactive protein probably have an indirect effect on the developing fetus because the protein does not pass the placenta [11]. The underlying pathways might include fetal growth restriction and smaller lungs and airways [12-14], a pro-inflammatory fetal or newborn status leading to cytokine deregulation, or other adaptations of the infant's immune system subsequently influencing the development of asthma [15, 16, 17]. Cord blood C-reactive protein levels reflect fetal levels and can have both direct effects, such as a TH2 skewed immune system, and indirect effects, as described for maternal C-reactive protein, on the fetus. Therefore, the timing of elevated C-reactive protein levels may have different effects on respiratory health of the child [18, 19, 20]. Thus far, the roles of maternal and cord blood C-reactive protein levels in the development of childhood asthma remain unclear.

2. Materials and methods

We examined in prospective study, among 32 children followed up from early fetal life, the associations between maternal and cord blood C-reactive protein levels with wheezing, respiratory tract infections in the first 1.5 years of life.

Maternal venous blood samples were collected in early pregnancy (median gestational age (13.5, 95% range 9.5 to 17.8 weeks) and fetal umbilical cord blood samples were collected by neonatologists immediately after delivery. High-sensitivity C-reactive protein levels were analyzed using an immunoturbidimetric method.

Statistics

During assessment of quantitative indicators, we were calculating mean and standard deviation (Std). In case of quantitative indicators reliability of differences between groups was determined by using student t criteria, when comparing we assessed dispersion equation by Levene's Test, selection of appropriate t criteria was done after obtained results. Mean frequency (%) was calculated for qualitative indicators, Differences between groups was assessed by –□2 criteria and by F(Fisher's) precise criteria. Correlations between factors were determined by Spearmen's rank correlation. The difference was thought to be reliable when $p<0.05$, mathematical provision was performed with use of software package SPSS22.

Results

Of the singleton live births (n=32), data on both maternal and cord blood C-reactive protein levels were available. wheezing , lower respiratory tract infections.

Table 1: Maternal Stress and C-reactive protein

		Stress	Light stress	Mild Stress	Severe Stress
CRP	r	-0.143	0.033	-0.228	-0.163
	p	0.435	0.860	0.210	0.374

Maternal C-reactive protein levels were not consistently associated with wheezing, lower respiratory tract infections in the child at the age of 1,5 y.

As compared to children from mothers with C-reactive protein levels in the lowest quarter, children from mothers in the highest quarter had an increased risk of wheezing until the age of 1.5 years.

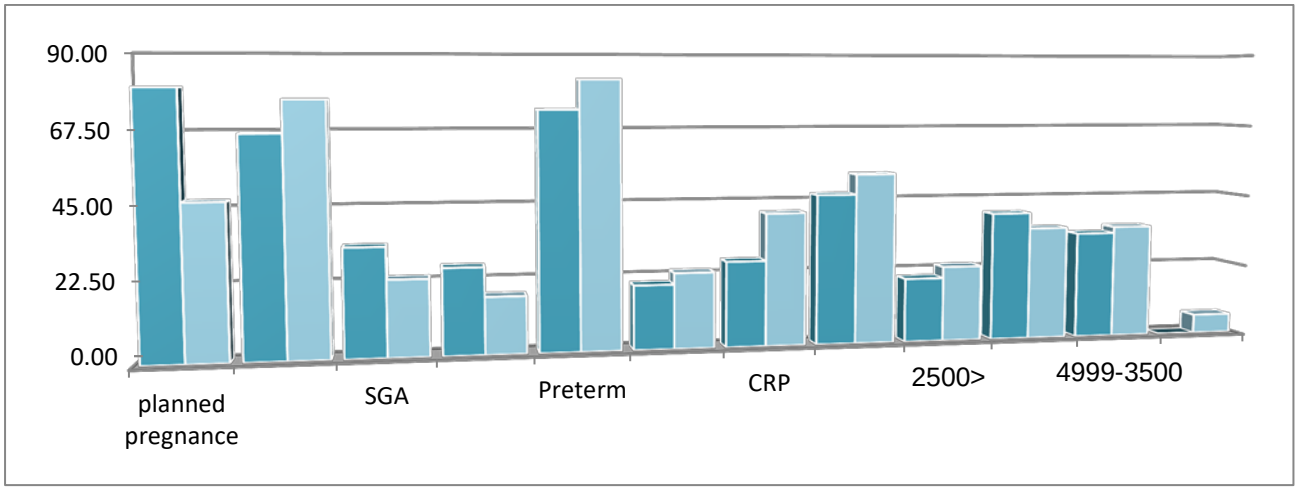

Figure1: Distribution of frequency(%) of newborn characteristics according to sex

During increased C-reactive protein level healthy term newborn is reliably less, and low birth weight newborn is reliably more compared to its gestation or w/o it, diagnosis of a newborn/RDS, weight <2500,

Frequency of wheezing morbidity according to cord blood C-reactive protein concentration is given in the diagram

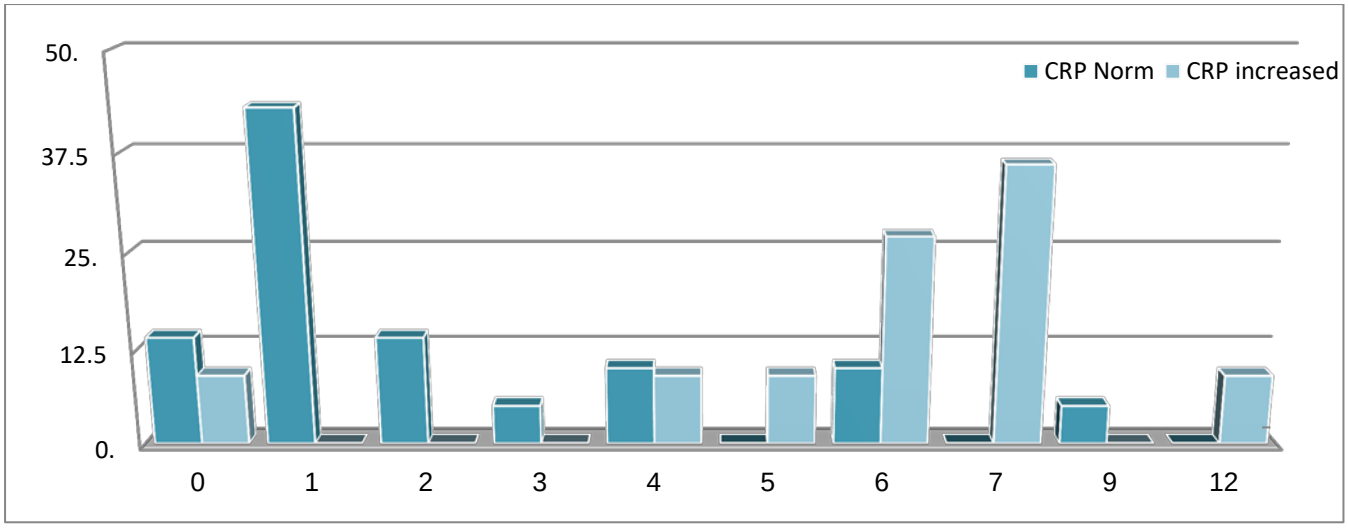

Figure 2: Distribution of frequency (%) of wheezing morbidity according to cord blood C-reactive protein (CRP) concentration

Morbidity with wheezing is reliably high in increased C-reactive protein group

According to ambulatory admission frequency there was no reliable difference between increased C-reactive protein group and normal level group

It is important to establish a link between newborn characteristics and cord blood C - reactive protein concentration, as well as a link between newborn characteristics itself, for diagnostic and prognostic purposes, what was done by correlation analysis.

Reliable positive correlation with C-reactive protein is seen with newborn low weight in comparison with gestation or w/o it - r=.572**; - p=0.001; newborn diagnosis/RDS - r=.413*; - p=0.019;; Referral - r=.572**; - p=0.001; morbidity with wheezing - r=.572**; - p=0.001; in-patient setting - r=.556**; - p=0.001; out-patient setting - r=.442*; - p=0.011; <2500 - r=.572**; - p=0.001.

Reliable negative correlation with C-reactive protein is seen with - - one newborn born in in-patient setting - r=-.425*; - p=0.015; term newborn - r=-.572**; - p=0.001; duration of breastfeeding - r=-.569**; - p=0.001;

Due to the concentration of C-Reactive Protein (CRP) in mother's blood no reliable differences have been revealed among wheezing frequent cases p 0,4481

Maternal C-reactive protein was not associated with the risks of wheezing and lower respiratory tract infections

3. Conclusion

Our results suggest that elevated Cord blood CRP levels are associated with wheezing and lower respiratory tract infections in the 1.5 years and predictive asthma young in life.

4. Discussion

Our results suggest that elevated maternal C-reactive protein levels in early pregnancy are not associated with risk of wheezing in the first 1.5 years and an overall higher risk of eczema, whereas cord blood C-reactive protein levels are associated with a higher overall risk of wheezing and lower respiratory tract infections. Previous studies suggested that children have a threefold increased risk of recurrent wheezing and a more than two fold increased risk of recurrent lower respiratory tract infections at the age of 14 months among children in the highest tertile compared to the lowest tertile of maternal C-reactive protein levels during pregnancy [10]. We observed a lower risk of wheezing in the first year for the highest maternal C-reactive protein levels group and no association of maternal C-reactive protein levels with lower respiratory tract infections. The C-reactive protein levels between the studies were measured during similar weeks of pregnancy and the 25%-75% ranges were comparable (2.0-7.0 mg/L vs. 2.3-7.7 mg/L for Morales and his colleagues and our study, respectively). Differences in the observed effects are unlikely to be the result of different laboratory methods (regular C-reactive protein levels vs. high sensitivity C-reactive protein levels) with different detection limits (2.0 mg/L vs. 0.2 mg/L, respectively) because both the lowest tertile and quartile reference group that were used included corresponding low C-reactive protein levels. A more likely explanation is that we assessed our outcomes annually and in a larger number of subjects, and were able to assess the influence of many potential effect modifiers. Pregnancy can be seen as an inflammatory stressor and elevated C-reactive protein levels with values of >10 mg/l are within the normal range for pregnant women throughout gestation. The highest quarter might have included mothers with an acute systemic inflammation and might have affected the strength of the associations. However, a sensitivity analysis excluding mothers with C-reactive protein levels >100 mg/L showed similar effect estimates. As we performed multiple tests, we cannot exclude that some results might be a chance finding. However, because of the correlation in outcomes we did not apply adjustment for multiple testing. The mechanisms explaining the relation between maternal C-reactive protein levels and a reduced risk of wheezing in the first year. The different direction of effect estimates between maternal and cord blood C-reactive protein levels may suggest that the timing of increased C-reactive protein levels is critical for the association with lung and airway development. Early adverse exposures might trigger developmental adaptations in the child, as suggested by the developmental origins hypothesis. This could lead to an adapted risk of respiratory symptoms. C-reactive protein cannot pass the placenta, thus the suggested association of maternal C-reactive protein levels and wheezing is not likely to be direct or causal. C-reactive protein is produced in the liver under IL-6 stimulation, and IL-6 may change the TH1/TH2 cell balance by inhibiting TH1 differentiation as well as promotion of TH2 differentiation [21]. A late exposure will not result in preventive adaptations, but we suggest that exposure to infections in late pregnancy makes the child more responsive to infections. The observed association between cord blood C-reactive protein and an early preschool wheezing pattern (supporting information) support the observed associations between cord blood C-reactive protein and wheezing and lower respiratory tract infections. Thus, increased cord blood C-reactive protein levels increase the risk of infections in the first four years of life. Also, after additional adjustment for lower respiratory tract infections the estimates attenuated into a non-significant effect. This suggests that the association between cord blood C-reactive protein and wheezing is, at least partly, explained by infectious mechanisms. Elevated C-reactive protein levels are suggested to be partially driven by an increased body mass index [22, 23]. Also, they are suggested to be associated with preeclampsia, subsequently leading to

increased risk of wheezing via an impaired placental functioning and its adverse effect on lung development [24, 27, 28]. However, in our study we did not observe these modifying effects. An elevated C-reactive protein level in cord blood might be the result of placental problems like inflammatory lesions [25, 26], a pro-inflammatory fetal or newborn status leading to cytokine dysregulation, or other adaptations of the infant's immune system subsequently influencing the development of infections and asthma [10]. We observed a modifying effect of gestational age at birth. The effect of elevated C-reactive protein levels on wheezing and lower respiratory tract infections were stronger in preterm than in term born children. This might be explained by a combined effect of an immature lung development.

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