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## **Total and Allergen Specific IgE Levels During and After Pregnancy in Relation to Maternal Allergy**

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**Abstract**

A Th2-skewed immunity may be necessary for a successful pregnancy and the ability to easily direct immune responses to a Th2-polarized profile may be an evolutionary benefit.

The Th2-like immunity associated with allergic disease might generate favourable effects on the maintenance of pregnancy, but also on the development of Th2-like immune responses and allergic disease in the offspring. The aim of this study was to explore, by using IgE as a stable proxy for Th2, the Th1/Th2 balance in allergic and non-allergic women by measuring specific and total IgE antibody levels during pregnancy and after delivery.

The specific and total IgE antibody levels were determined by ImmunoCAP technology at five occasions during pregnancy (at gestational week 10-12, 15-16, 25, 35 and 39), as well as 2 and 12 months after delivery. Thirty-six women without and 20 women with allergic symptoms were included, of whom 13 were sensitised with allergic symptoms and 30 non-sensitised without allergic symptoms.

The levels of total IgE, but not specific IgE, were increased during early pregnancy, as compared to 12 months after delivery, in the sensitised women with allergic symptoms, but not in the non-sensitised women without allergic symptoms ( $p < 0.01$ ). The increase in total IgE levels during early pregnancy only in the sensitised women with allergic symptoms indicates that allergy is associated with an enhanced Th2 deviation during pregnancy.

**Keywords:** Allergy, IgE, Phadiatop, pregnancy, Th2

## 1. Introduction

The human fetus expresses paternal alloantigens and may therefore be regarded as foreign by the maternal immune system. The fetus is normally not rejected, probably due to multiple protective mechanisms, but the current understanding of the establishment and maintenance of the immunological tolerance in human pregnancy is not complete.

During the last 15 years, pregnancy has been described as a Th2-phenomenon, with high levels of type 2 T-helper (Th2)-like cytokines at the fetomaternal interface (Wegmann et al. 1993), probably in order to divert the maternal immune response away from damaging type 1 T-helper (Th1)-mediated immune responses (Piccinni et al. 1998). Pregnant women have shown an increased number of interferon- $\gamma$  (IFN- $\gamma$ ) and **interleukin-4** (IL-4) secreting peripheral blood mononuclear cells (PBMC) cells as compared to after delivery (Matthiesen et al. 1998; Matthiesen et al. 2003; Persson et al. 2008). Furthermore, stimulation with paternal leukocytes increases the secretion of IL-4 by maternal PBMC during normal pregnancy (Ekerfelt et al. 1997). Previous studies have reported a high secretion of Th2-like cytokines at the time of delivery of normal pregnancies and increased Th1-like cytokines at the time of a spontaneous abortion (Marzi et al. 1996; Makhseed et al. 2001). Taken together, a local as well as a systemic Th2-deviation during pregnancy may be necessary for a successful pregnancy and the ability to easily direct immune responses to a Th2-polarized profile may be an evolutionary benefit.

Allergic diseases are associated with high IgE antibody levels and expression of the allergen induced Th2-like cytokines IL-4, IL-5 and IL-13 (Robinson et al. 1992; Mazzearella et al. 2000; Gould et al. 2003). IL-4 and IL-13 induce IgE synthesis (Punnonen et al. 1993) and IL-5 causes allergic inflammation by promoting eosinophil maturation (Egan et al. 1996).

Regulatory T cells (Treg) are able to suppress Th1 as well as Th2 activity, and an impaired Treg function has been suggested to contribute to the disease (Ling et al 2004). Th17 cells and

their inflammatory mediators attract and promote neutrophil development, and are not known to drive Th2 responses, implying a role for Th17 cells in non-allergic asthma (reviewed in Oboki et al. 2008). The role of Th17 cells in allergy is not clear, and needs further investigation.

Allergic disease is associated with shorter waiting time to pregnancy (Westergaard et al. 2003), longer gestational age, higher birth weight (Somoskovi et al. 2007) and less pre-term births (Savilahti et al. 2004). Thus, the Th2-like immunity associated with allergic disease might generate favourable effects on the likelihood of being pregnant and the maintenance of pregnancy.

The higher cord blood (CB) IgE levels seen in newborns of allergic mothers, as compared to newborns with a paternal or no allergic history (Magnusson 1988; Johnson et al. 1996; Liu et al. 2003), may possibly depend on a stronger Th2 shift at the feto-maternal interface of allergic mothers, although this has not been investigated. The Th2 polarisation during pregnancy may influence the offspring for variable periods postnatally. As the cytokine milieu at the priming of T cells direct the Th1/Th2 differentiation (Demeure et al. 1994), the gestational environment could be very important for shaping immune responses. In support of this, a murine allergy model demonstrated that enhanced Th2-like immunity during pregnancy strongly influenced the shaping of the Th1/Th2 profile in the neonate (Herz et al. 2000).

Newborn mice from ovalbumin sensitised mothers showed a decreased ability to produce the Th1-like cytokine IFN- $\gamma$ , higher frequency and higher titers of IgG<sub>1</sub> antibodies to  $\beta$ -lactoglobulin after  $\beta$ -lactoglobulin injection (Herz et al. 2000). These results indicate that prenatal exposure to a Th2-like environment favours the development of Th2-like immune responses in the offspring. Also in humans, maternal sensitisation to allergens was associated with a reduced maternal production of the Th-2 antagonist IFN- $\gamma$  and elevated production of the Th2-like cytokine IL-13 in the newborn baby (Kopp et al. 2001).

To further explore the Th1/Th2 balance in allergic and non-allergic women during pregnancy, we used IgE as a stable proxy for Th2 and examined changes in total IgE and allergen specific IgE antibodies during pregnancy in a group of 20 pregnant women with allergic symptoms and 36 pregnant women without allergic symptoms. We hypothesise that immune responses will be biased towards a Th2-like profile during pregnancy in both groups, with a more pronounced deviation in the allergic group.

## 2. Materials and methods

### 2.1 Study group

The study comprised 20 pregnant women with allergic symptoms and 36 pregnant women without allergic symptoms from the Linköping area, County of Östergötland, Sweden. Due to technical and practical reasons, it was not possible to perform this study with a larger number of participants. The allergic status was established by a typical clinical history, *i.e.* symptoms of allergic rhinoconjunctivitis (ARC, n=17), asthma (n=4 of whom 1 also had ARC) or eczema (n=2, both had also ARC). An experienced allergy research nurse interviewed the women using structured questionnaires. The allergic status of the women were further determined using the Phadiatop<sup>®</sup> test (see below) and the women were divided into two groups, 13 women were sensitised with allergic symptoms (sensitised according to Phadiatop testing combined with a history of allergic symptoms) and 30 women were non-sensitised without allergic symptoms. The pregnant women were recruited by convenience sampling *i. e.* among women attending the maternity health care clinic in Linköping. All women gave their informed consent to participate in the study. Data on maternal and neonatal characteristics is shown in table 1. Plasma samples were collected at 5 occasions during pregnancy (at gestational week 10-12, 15-16, 25, 35 and 39), as well as 2 months and 1 year after the delivery. Unfortunately, plasma samples were not available for all women at all occasions. All plasma samples were frozen and stored at -70°C.

### 2.2 Phadiatop<sup>®</sup>

The total concentration of specific IgE antibodies directed to common inhalant allergens from birch, mugwort, timothy, cat, dog, horse, house-dust mite, (*Dermatophagoides pteronyssinus* and *farinae*), *Cladosporium* was measured with the Phadiatop<sup>®</sup> test and expressed as a qualitative result, either positive or negative. The cut-off for positivity was

0.35 kU<sub>A</sub>/l, corresponding to a fluorescence intensity of 168 response units (RU). The undiluted plasma samples from the allergic and non-allergic pregnant women were analysed by the Phadiatop<sup>®</sup> test using the ImmunoCAP technology (UniCAP 100) according to the manufacturer's instructions (Pharmacia Diagnostics, Uppsala, Sweden).

*Table 1. Maternal and neonatal characteristics*

<u>Maternal characteristics</u> <u>median (range)</u>	Women with allergic symptoms (n=20)	Women without allergic symptoms (n=36)
Maternal age at delivery (yr)	31 (24-38)	31 (22-40)
Body Mass Index at gwk 10	23 (18-32)	24 (19-34)
Gestational age (wk)	40 (38-42)	40 (34-42)
<u>Maternal characteristics</u> <u>number</u>		
Previous successful pregnancies	primiparous n=10, parous n=10	primiparous n=14, parous n=22
Caesarean section	n=3	n=7
Smoking during pregnancy	n=1	n=6
<u>Neonatal characteristics</u> <u>median (range)</u>		
Birth length (cm)	51,5 (48-54)	51 (45-54)
Birth weight (g)	3815 (3000-4490)	3650 (2580-4210)
<u>Neonatal characteristics</u> <u>number</u>		
Sex	boys n=13, girls n=7	boys n=19, girls n=17

yr=years, wk=weeks, gwk=gestational week. There are no significant differences between the groups regarding the maternal and neonatal characteristics, shown in the table. Data regarding Body Mass Index was missing for 1 woman without allergic symptoms and regarding smoking habits during pregnancy for 1 woman without allergic symptoms.

### 2.3 Total IgE antibody analysis

The total IgE concentrations in the plasma samples were analysed by the immunoassay system ImmunoCAP. The manufacturer's recommendations were followed and the results were expressed as kU/l. The detection limit of the total IgE assay was 2 kU/l.

## **2.4 Statistics**

Non-parametric tests, corrected for ties, were used. Friedman's test was used to investigate if the concentration of IgE antibodies changed during pregnancy and the year after delivery.

Wilcoxon's signed rank test was used to investigate if there were any differences in the IgE levels between different time points, and comparisons between unpaired groups were performed by the Mann-Whitney *U*-test. The Chi-squared test was used for categorical variables and Fisher's exact test was used when the expected frequency for any cell was less than 5. The calculations were made with the statistical package SPSS 14.0 for Windows (SPSS Inc, Chicago, IL, USA) and Stat View for Windows Version 5.9 (SAS Institute Inc., Cary, North Carolina, USA).

## **2.5 Ethics**

The study was approved by the Regional Ethics Committee for Human Research at the University Hospital of Linköping.

### **3. Results**

#### **3.1 Occurrence of specific IgE antibodies during pregnancy in relation to maternal allergic symptoms**

The presence of allergen specific IgE antibodies at five occasions during pregnancy (at gestational week 10-12, 15-16, 25, 35 and 39), 8 weeks and 12 months after delivery was measured with the Phadiatop test in a group of 20 women with allergic symptoms and 36 women without allergic symptoms. No significant changes in fluorescence intensity between the pregnancy and one year after delivery were shown for any of the groups (Figure 1).

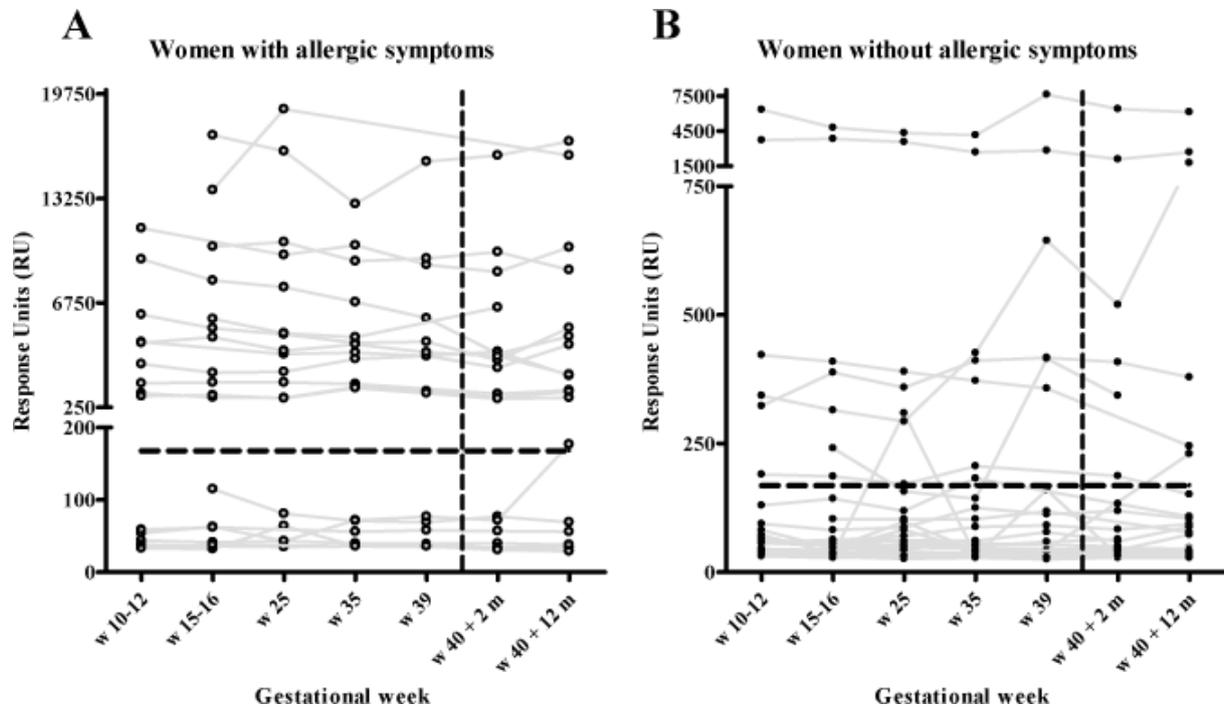
Most of the women with allergic symptoms (Figure 1 a) showed, as expected, much higher fluorescence intensities, than the women without allergic symptoms ( $p < 0.01$ - $p < 0.001$ , Figure 1 b). Using more strict criteria for allergic disease, neither sensitised women with allergic symptoms ( $n=13$ ) nor non-sensitised women without allergic symptoms ( $n=30$ ) showed any significant changes in fluorescence intensity over the analysed time (Friedman's test).

#### **3.2 Total IgE antibody levels during pregnancy in sensitised women with allergic symptoms and non-sensitised women without allergic symptoms**

The concentration of total IgE antibodies was measured at five occasions during pregnancy, as well as 8 weeks and 12 months after delivery in 13 sensitised women with allergic symptoms and 30 non-sensitised women without allergic symptoms. Sensitised women with allergic symptoms displayed IgE concentrations in the range of 12 to 464 kU/l and the non-sensitised women without allergic symptoms between 1 and 112 kU/l (Figure 2,  $p < 0.01$ - $p < 0.001$  at the various time points, Mann-Whitney U-test).

Total IgE levels changed over the analysed time period in the sensitised women with allergic symptoms (Figure 2a,  $p < 0.01$ , Friedman's test), but not in the non-sensitised women without allergic symptoms (Figure 2b). The total IgE levels decreased from gestational week 10-12 to

12 months after delivery in the sensitised women with allergic symptoms ( $p < 0.01$ , Wilcoxon signed rank test, **Figure 3a**) but not in the non-sensitised women without allergic symptoms (**Figure 3b**).



*Figure 1. Fluorescence intensities (response units, RU) generated from the Phadiatop test at 5 occasions during pregnancy as well as 2 months and 1 year after delivery in (A) women with allergic symptoms and (B) women without allergic symptoms. The cut-off for positive results is marked by a thick dotted line. Thirteen of the 20 women with allergic symptoms were also sensitised and 30 of the 36 women without allergic symptoms were non-sensitised.*

The same pattern was shown in the 20 women with allergic symptoms (regardless of Phadiatop status), but not in the 36 women without allergic symptoms. The total IgE levels decreased from 10 weeks pregnancy to 12 months after delivery in the women with allergic symptoms ( $p < 0.05$ , Wilcoxon signed rank test).

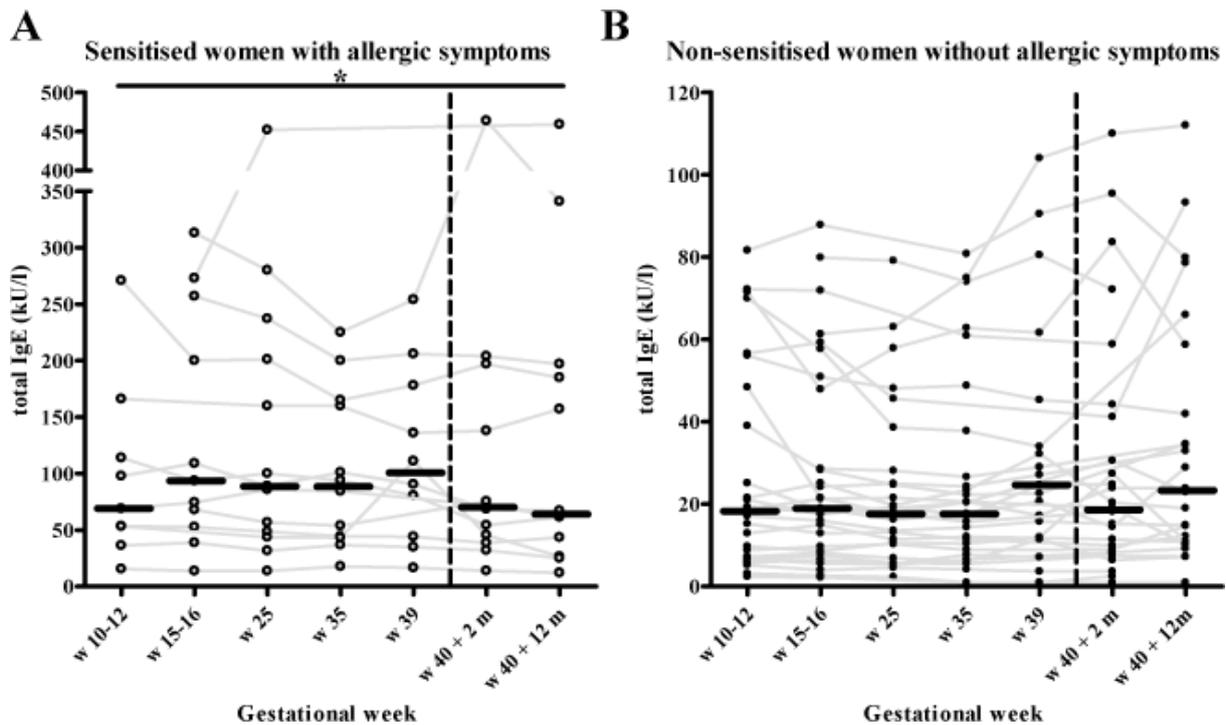


Figure 2. The total concentration of IgE antibodies measured at 5 occasions during pregnancy, 2 months and 1 year after delivery in (A) sensitised women with allergic symptoms (B) non-sensitised women without allergic symptoms. The median (absolute level at each time point) is marked with lines. The total IgE levels decreased from 10 weeks pregnancy to 12 months after delivery in the sensitised women with allergic symptoms (\* =  $p < 0.01$ ).

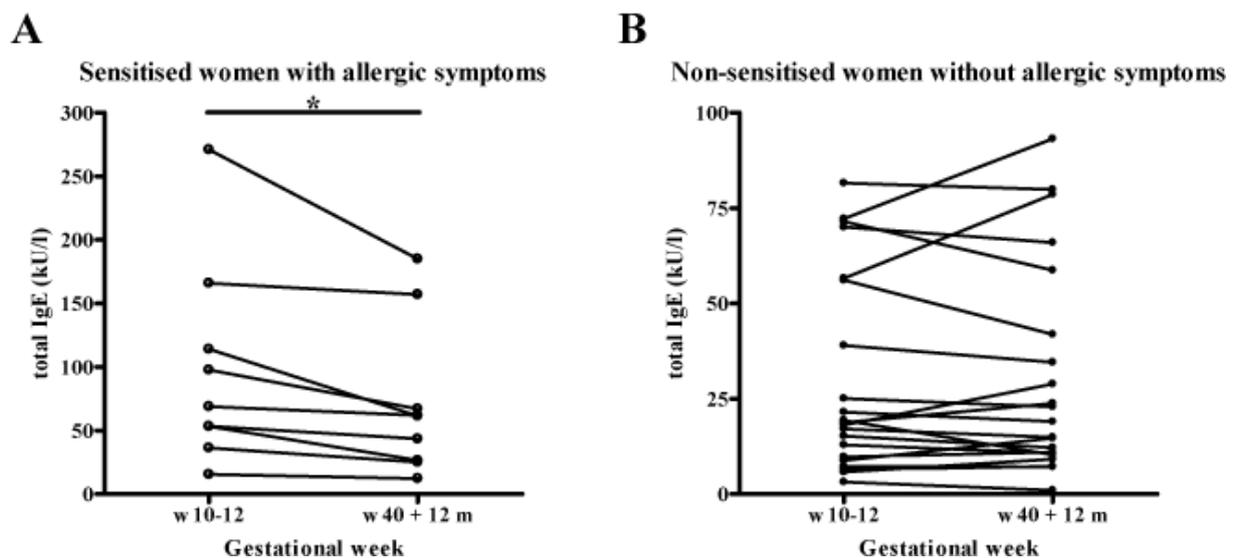


Figure 3. The total IgE levels were increased at gestational week 10-12 as compared to 12 months after delivery in (A) sensitised women with allergic symptoms but not in the (B) non-sensitised women without allergic symptoms. (\* =  $p < 0.01$ ).

#### 4. Discussion

In the present study, we found that the levels of total IgE were increased during early pregnancy in the sensitised women with allergic symptoms, but not in the non-sensitised women without allergic symptoms. The total IgE levels decreased from 10 weeks pregnancy to 12 months after delivery in the sensitised women with allergic symptoms. Although the change was quite modest in absolute levels, all sensitised women with allergic symptoms showed a decreased concentration one year postpartum as compared to early pregnancy (gestational week 10-12). This change in total IgE concentration was not observed in the non-sensitised women without allergic symptoms, and may thus depend on a stronger Th2 shift during pregnancy in the sensitised mothers with allergic symptoms. The enhanced Th2-like immunity might generate favourable effects on the maintenance of pregnancy (Savilahti et al. 2004; Somoskovi et al. 2007), but also on the development of Th2-like immune responses in the offspring. Newborns of allergic mothers have shown higher CB IgE levels as compared to newborns with a paternal or no allergic history, possibly related to a more pronounced Th2 deviation during pregnancy in allergic mothers (Magnusson 1988; Johnson et al. 1996; Liu et al. 2003). Furthermore, maternal, but not paternal IgE levels correlate with CB IgE levels (Liu et al. 2003).

Our findings are in agreement with previously published data showing significantly increased total IgE levels in the third trimester compared to 2 years postpartum in a group of allergic pregnant women (Amoudruz et al. 2006). The IgE levels were reported only at one occasion during pregnancy in that study, however. Furthermore, that study raises the question if the observed increase in total IgE concentration during pregnancy in the allergic women is caused by an increase in specific IgE levels and if that is the case, if the concentrations of specific IgE will follow the decrease of total IgE. To address this question, we measured the levels of IgE antibodies to a panel of common inhalant allergens during and after pregnancy and we

did not observe any changes in levels of specific IgE antibodies in the sensitised women with allergic symptoms or non-sensitised women without allergic symptoms over time (Friedman's test). Our results indicate that enhanced IgE responses to allergens did not cause the increase in total IgE levels during pregnancy. It is more likely that the increase in total IgE levels in sensitised women with allergic symptoms depends on a stronger general Th2 shift during pregnancy.

Immunoglobulin (Ig) levels are not generally increased during pregnancy. Two studies have shown strongly decreased levels of IgG during pregnancy (first and third trimester and gestational week 12, 24, 36) and elevated levels postpartum (Yasuhara et al. 1992; Ailus 1994). The IgM and IgA levels were slightly decreased during pregnancy and increased postpartum, *i.e.* a similar pattern to the IgG levels (Yasuhara et al. 1992; Ailus 1994). When hemodilution was taken to account, increased levels of IgM and IgA were observed in the third trimester, whereas the decrease in IgG levels during pregnancy disappeared (Ailus 1994). The Ig levels were not tested for any relationship to maternal allergic disease in these studies, however. As the decrease in IgG levels showed in these studies is most likely a result of hemodilution, our finding of increased IgE levels during pregnancy becomes even more remarkable.

Seasonal exposure to *e.g.* pollen influences IgE antibody levels in allergic individuals (Lagier et al. 1995). This phenomenon is not considered to be a confounding factor in our study, since no changes in specific IgE antibody levels in the sensitised women with allergic symptoms or non-sensitised women without allergic symptoms were detected over time, and the first collection of plasma samples occurred between the middle of November and middle of March for 8 of 9 samples available at this time point from the 13 sensitised women with allergic symptoms. The first collection of plasma was gathered during the pollen season (end of June) for one allergic woman sensitised to grass pollen. The total IgE levels were significantly

higher at 10 weeks of pregnancy than 12 months after delivery, even when this woman was excluded. Other potential confounding factors such as smoking and number of previous pregnancies did not affect the IgE levels in this study (Mann-Whitney U-test). **The incidence and extent of allergy medication during the analysed period were unfortunately not available and we can not exclude the possibility of a confounding effect, even though common anti-allergic drugs like anti-histamines generally do not influence the IgE levels (Lee et al. 2008). The asthmatic women in our study were not sensitised.** The IgE levels 12 months post partum has been used as a surrogate reference point of time, in relation to the IgE levels during pregnancy. Although a pre-pregnancy state would be most optimal in reflecting the baseline, it was not, due to obvious reasons, possible to conduct such study. The non-sensitised women without allergic symptoms should, according to our hypothesis, show a Th2 skewed immunity during pregnancy, although less strong compared to the allergic group. Our IgE data do not indicate such a Th2 shift in the non-sensitised women without allergic symptoms, but support the idea of an association of allergy with a more pronounced Th2 deviation during pregnancy. The observed Th2 shift in early pregnancy might be caused by an enhanced ability of allergic individuals to direct immune responses to a Th2-polarized profile.

Several studies have shown an elevated production of Th2-like cytokines and a decrease in Th1-like cytokines during normal pregnancies compared to pathological pregnancies (Marzi et al. 1996; Raghupathy et al. 2000; Makhseed et al. 2001). The distinct Th2-bias during normal pregnancies showed in these studies could be enhanced as a consequence of a control group including both non-allergic and allergic individuals. It is possible that allergic individuals are included in the group of pathological pregnancies as well, possibly reducing the observed Th1-bias in the women undergoing recurrent spontaneous abortions. Our study

clearly demonstrates that it is very important to determine the allergic status of the pregnant women when the Th1/Th2 balance is studied in relation to pregnancy.

A more Th2-skewed response during pregnancy, characterized by high IgE levels, might influence the Th1/Th2 profile in the neonate. We have previously observed positive correlations between maternal IgE levels, CB IgE and CCL22 (macrophage derived chemokine MDC) levels and increased CCL22 (MDC) levels at birth was, as well as increased CB IgE levels, associated with development of allergic disease during the first 2 years of life in the offspring (Sandberg et al. in press).

In conclusion, the decrease in total IgE levels 1 year after delivery only in the sensitised women with allergic symptoms indicates that allergy is associated with a more pronounced Th2 deviation during pregnancy. The Th2 polarisation during pregnancy might affect the shaping of the Th1/Th2 profile in the neonate and hypothetically the development of allergic diseases later in life.

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