

REGULAR ARTICLE

# Placental inflammation, lifestyle, maternal and early child sensitisation to allergens – the assessment of lifestyle and allergic disease during infancy birth cohort

Nikos Papadogiannakis<sup>1</sup>, Maaïke Joerink<sup>2,\*</sup>, Erika Rindsjö (erika.rindsjo@ki.se)<sup>3</sup> , Annika Scheynius<sup>4,5</sup>, Johan Alm<sup>4</sup>

1.Department of Laboratory Medicine, Division of Pathology, Section of Perinatal Pathology, Karolinska Institutet and Karolinska University Hospital Huddinge, Stockholm, Sweden

2.Translational Immunology Unit, Department of Medicine Solna, Karolinska Institutet and University Hospital, Stockholm, Sweden

3.Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

4.Department of Clinical Science and Education, Sachs' Children and Youth Hospital, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

5.Clinical Genomics, Science for Life Laboratory, Stockholm, Sweden

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Home delivery, Lifestyle, Placenta, Placental inflammation, Sensitisation

## Correspondence

Erika Rindsjö, Department of Oncology-Pathology, Karolinska Institutet, 171 76 Stockholm, Sweden.

Tel: +46-8-51774166 |

Fax: +46-8-51770690 |

Email: erika.rindsjo@ki.se

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\*In memoriam.

## ABSTRACT

**Aim:** To investigate (i) whether maternal sensitisation to allergens, and lifestyle can influence the risk of acute and chronic inflammation of the placenta, in the forms of chorioamnionitis and villitis, respectively, and (ii) whether these placental inflammations are associated with the outcome of sensitisation for the child during preschool age.

**Methods:** Placentas from term uncomplicated pregnancies ( $n = 275$ ) in the assessment of lifestyle and allergic disease during infancy study were analysed for the presence of acute chorioamnionitis and chronic villitis. Stepwise logistic regression was performed to estimate the relative risk of placental inflammation in relation to maternal allergic sensitisation and lifestyle, and the association between placental inflammation and sensitisation of the child up to five years of age.

**Results:** Parity and delivery at home were independently associated with chorioamnionitis, home delivery only with the low grade. Maternal allergic sensitisation was associated with increased risk of villitis in the bivariable model, however, not in the multivariable model. No significant associations were detected between placental inflammation and the outcome of sensitisation to allergens at five years of age.

**Conclusion:** Our data do not support the hypothesis that the increased risk for sensitisation of a child when the mother is allergic is mediated via placental inflammation.

## INTRODUCTION

Acute chorioamnionitis is defined histologically by the accumulation of maternal polymorphonuclear leucocytes in placental membranes and is generally considered as a marker for clinical or subclinical intrauterine infection, commonly bacterial (1). Most cases are, however, subclinical without any maternal symptoms (2). Chorioamnionitis is a major cause of preterm labour, preterm premature rupture of membranes and it is strongly associated with perinatal morbidity and mortality (3). In preterm infants, chorioamnionitis correlates both with a decreased risk of respiratory distress syndrome and an increased risk of chronic lung disease (3–5). Risk factors for chorioamnionitis are nulliparity, spontaneous labour, longer total duration of labour and maternal asthma (6–8).

Villitis is in contrast to chorioamnionitis a chronic inflammation. It is characterised by infiltration of maternal T lymphocytes and foetal macrophages in the villous stroma (9). In rare cases, it can be caused by infection, but a large proportion of cases has unknown aetiology, termed villitis of unknown aetiology (9). It has been suggested that villitis

of unknown aetiology has an immunological origin and is analogous to either an allograft rejection or a placental graft versus host disease (10). Villitis has been reported to be associated with small for gestational age and intrauterine growth restriction (9,11). Risk factors for villitis of

## Key notes

- This study explores links between placental inflammation, maternal sensitisation to allergens, lifestyle and early child sensitisation in a unique cohort (assessment of lifestyle and allergic disease during infancy) of term uncomplicated pregnancies.
- Parity and delivery at home were independently associated with chorioamnionitis, home delivery only with the low grade.
- The results do not support the hypothesis that the increased risk for sensitisation of a child when the mother is allergic is mediated via placental inflammation.

unknown aetiology are maternal obesity, multigravidity and previous villitis (9,11). There are no reported associations between chronic villitis and maternal allergy/allergic disease, although in both cases underlying dysregulation or imbalance of maternal immune system is implied.

The intrauterine environment plays an important role for the risk of allergy and asthma development of the child (12–14). In addition, lifestyle can influence this risk since children growing up on a farm or with an anthroposophic lifestyle have a reduced prevalence of sensitisation and allergic disease (15–18). Maternal asthma and allergy have been reported to confer a higher risk for development of asthma and allergy in children than paternal asthma and allergy (19,20). Interestingly, maternal asthma has been indicated as a risk factor for chorioamnionitis (6) while chorioamnionitis at preterm gestation also has been shown to be associated with increased risk of physician-diagnosed asthma in childhood (21,22). We hypothesised that these associations between maternal asthma, child asthma and chorioamnionitis could represent a more general mechanism in which maternal sensitisation and lifestyle via placental inflammation influence the development of the foetal immune system and thus the risk of allergy development later in life. The aim of this study was to investigate (i) whether maternal sensitisation to allergens, and lifestyle can influence the risk of acute and chronic inflammation of the placenta, in the forms of chorioamnionitis and villitis, respectively, and (ii) whether these placental inflammations are associated with the outcome of sensitisation for the child during preschool age.

## MATERIALS AND METHODS

### Study population and collection of placenta

Pregnant women ( $n = 330$ ) were recruited during 2004–2008 to the assessment of lifestyle and allergic disease during infancy (ALADDIN) study, from anthroposophic and conventional maternal-child health centres in the Stockholm area, Sweden (18). A questionnaire filled out by the parents two months after the birth of the child, was used to determine the lifestyle (anthroposophic, partly anthroposophic, or non-anthroposophic) of the families as described before (18). After delivery, 282 placentas were transported on ice to the laboratory and two placenta biopsies, one next to the umbilical cord and one at the periphery about 0.5 cm thick and spanning the whole thickness of the placenta, a piece of the membranes, and of the umbilical cord were washed with PBS, fixed in formalin and paraffin-embedded. In four cases, inadequate material was sampled from placenta or umbilical cord, and information on lifestyle was lacking for three mothers, leaving 275 placentas to be finally analysed. Inclusion criteria for this study were: information of lifestyle/normal/healthy/uncomplicated pregnancy and delivery at  $\geq 35 + 0$  weeks of gestation.

This study was approved by the Regional Ethical Review Board, Karolinska Institutet, Stockholm, Sweden, and all parents gave their written informed consent.

### IgE serology

Maternal blood samples were collected during the third trimester and for the child at six months, one, two and five years of age. Plasma was used to determine sensitisation. Maternal sensitisation was defined as having a positive allergen-specific plasma IgE measurement ( $\geq 0.35$  kU<sub>A</sub>/L) to a mix of 11 common airborne allergens (Phadiatop™; Thermo Fisher Scientific, Uppsala, Sweden) while non-sensitised was defined as being Phadiatop™ negative ( $< 0.35$  kU<sub>A</sub>/L). Children were regarded sensitised when their plasma IgE levels at six months, one and/or two years, against at least one of seven allergens (egg white, milk, peanut, cat, dog, timothy or birch) was  $\geq 0.35$  kU<sub>A</sub>/L, as measured by ImmunoCAP™ (Thermo Fisher Scientific) while non-sensitised children had plasma IgE levels  $< 0.35$  kU<sub>A</sub>/L for all seven allergens. At 60 months, a food mix (fx5) and Phadiatop™ were used, adding the allergens codfish, wheat flour, soybean, and *Cladosporium*, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, horse and mugwort (all kits from Thermo Fisher Scientific). Allergen-specific IgE levels  $\geq 0.35$  kU<sub>A</sub>/L were categorised as IgE-sensitisation.

### Analysis of placenta

All placental samples were submitted to routine histopathological examination and evaluated on haematoxylin and eosin-stained formalin-fixed sections by a senior perinatal pathologist (NP), under coded conditions. Acute chorioamnionitis was assessed on a three-grade scale, as follows: grade 1 or low grade: presence of polymorphonuclear leucocytes at the subchorionic plate and/or lower third of chorion; grade 2: at least two separate foci of leucocyte infiltration on chorion and amnion; and grade 3: extensive leucocyte infiltration in chorion and amnion, together with necrosis of amniotic epithelium and/or microabscess formation (23). The presence of polymorphonuclear leucocytes in vessel wall (vasculitis) in umbilical cord and chorionic plate was additionally noted. Chronic villitis was defined as the presence of mononuclear cell infiltrate in villous stroma and recorded without any quantification of the lesions. Foci of villitis are usually limited to  $< 1\%$  of the placenta. Previous results indicate that the presence of villitis *per se* rather than its extent in the placenta may be associated with foetal pathology (24).

### Statistical analysis

Fisher's exact test was used to estimate associations between binary variables. Kruskal–Wallis test was used if one of the two variables were continuous. Logistic regression was used to estimate the odds ratios (ORs) in bivariate and multivariate models. In the bivariate models, the following three variables: maternal sensitisation, parity and birthplace were separately combined with lifestyle. In the multivariate models maternal sensitisation, family lifestyle, parity, birthplace, delivery mode, maternal age, sex of the child, living on a farm and maternal smoking during pregnancy were analysed, all in the same model. Statistical analysis was conducted using IBM SPSS Statistics 23

(Armonk, NY, USA).  $p \leq 0.05$  was accepted as being statistically significant.

## RESULTS

Demographic and exposure factors are shown in Table 1 of which parity, home delivery, delivery mode and gestational age at birth differed significantly between the three lifestyle groups, as well as sensitisation during infancy.

Of the 275 placentas histologically investigated 274 were assessable regarding chorioamnionitis, which was present in 42% (24% grade 1, 16% grade 2 and 2% grade 3; data not shown). Logistic regression was used to determine associations between maternal sensitisation, family lifestyle, parity, birthplace and the risk of any chorioamnionitis versus no chorioamnionitis (Table 2). The analyses did not reveal any significant associations except for parity which was highly inversely associated with chorioamnionitis in both models; OR 0.59,  $p = 0.001$  in the bivariate model, and OR 0.54,  $p < 0.001$  in the multivariate model (Table 2).

When analysing low-grade chorioamnionitis versus no chorioamnionitis, no significant associations were detected in the bivariate model, except for parity (OR 0.64,

$p = 0.022$ ). In the multivariable model, besides an inverse association with parity (OR 0.58,  $p = 0.011$ ), delivery at home was significantly and independently associated with risk of low-grade chorioamnionitis (OR 2.4,  $p = 0.046$ ). Because only few ( $n = 5$ ) placentas had chorioamnionitis grade 3 these were pooled with grade 2 into the group high-grade chorioamnionitis. Analysis of high-grade chorioamnionitis versus no chorioamnionitis revealed significant associations in both the bivariate and multivariable models for parity (OR 0.51,  $p = 0.003$  and OR 0.47,  $p = 0.001$ , respectively).

To analyse the association between maternal sensitisation, or lifestyle and a chronic placental inflammation the presence of villitis was analysed (Table 2). Villitis was detected in 12% of the 275 placentas. We identified a significant association between maternal sensitisation and villitis in the bivariate model (OR 2.2,  $p = 0.032$ ), which, however, was no longer significant in the multivariate model (Table 2).

The intrauterine environment plays an important role for the risk of allergy development for the child (13,14). We therefore analysed the association between the presence of chorioamnionitis or villitis and the child's sensitisation to

**Table 1** Demographic and exposure factors for children from families with an anthroposophic, partly anthroposophic and non-anthroposophic lifestyle [Categorical variables: n/N (%), continuous variables: median (min–max)]

|                                                             | Anthroposophic<br>N = 72 | Partly anthroposophic<br>N = 112 | Non-anthroposophic<br>N = 91 | p*     |
|-------------------------------------------------------------|--------------------------|----------------------------------|------------------------------|--------|
| Mother's age <sup>†</sup> , years                           | 32 (18–50)               | 31 (19–42)                       | 32 (20–42)                   | 0.37   |
| Parity                                                      | 2 (1–5)                  | 2 (1–4)                          | 2 (1–4)                      | 0.017  |
| Mother $\geq 1$ t/w <sup>‡</sup> in stable during pregnancy | 8/68 (11.8)              | 8/107 (7.5)                      | 10/85 (11.8)                 | 0.49   |
| Maternal smoking during pregnancy                           | 4/70 (5.7)               | 6/110 (5.5)                      | 8/88 (9.1)                   | 0.58   |
| Maternal IgE-sensitisation <sup>§</sup>                     | 17/72 (23.6)             | 33/112 (29.5)                    | 28/91 (30.8)                 | 0.59   |
| Delivery place                                              |                          |                                  |                              |        |
| Hospital                                                    | 38/71 (53.5)             | 83/111 (78.4)                    | 88/88 (100.0)                | <0.001 |
| Home                                                        | 33/71 (46.5)             | 28/111 (25.2)                    | 0/88 (0.0)                   |        |
| Delivery mode                                               |                          |                                  |                              |        |
| Vaginal                                                     | 65/71 (91.5)             | 106/111 (95.5)                   | 72/88 (81.8)                 | 0.005  |
| Section                                                     | 6/71 (8.5)               | 5/111 (4.5)                      | 16/88 (18.2)                 |        |
| Gestational age <sup>¶</sup> , weeks                        | 40 (36–43)               | 40 (36–42)                       | 39 (35–42)                   | 0.003  |
| Birth weight, g                                             | 3705 (2350–4650)         | 3598 (2660–5320)                 | 3515 (2370–4790)             | 0.13   |
| Girls                                                       | 34/72 (47.2)             | 57/112 (50.9)                    | 48/90 (53.3)                 | 0.75   |
| Living on a farm at birth                                   | 12/69 (17.4)             | 7/108 (6.5)                      | 9/87 (10.3)                  | 0.19   |
| Having older siblings <sup>  </sup>                         | 53/68 (77.9)             | 67/108 (62.0)                    | 59/86 (68.6)                 | 0.087  |
| Child sensitised at                                         |                          |                                  |                              |        |
| 6 months of age <sup>**</sup>                               | 1/47 (2.1)               | 7/76 (9.2)                       | 14/71 (19.7)                 | 0.009  |
| 1 year of age <sup>**</sup>                                 | 1/40 (2.5)               | 11/81 (13.6)                     | 22/73 (30.1)                 | <0.001 |
| 2 years of age <sup>**</sup>                                | 8/54 (14.8)              | 12/83 (14.5)                     | 20/80 (25.0)                 | 0.18   |
| 5 years of age <sup>††</sup>                                | 12/45 (26.7)             | 21/76 (27.6)                     | 25/61 (41.0)                 | 0.19   |

\*Fisher's exact test for categorical variables, Kruskal–Wallis test for continuous variables.

<sup>†</sup>At delivery.

<sup>‡</sup>Time per week.

<sup>§</sup>Plasma IgE  $\geq 0.35$  kU<sub>A</sub>/L to a mix of 11 common airborne allergens, Phadiatop™ (Thermo Fisher Scientific).

<sup>¶</sup>National Birth Register, 'completed weeks best estimation'.

<sup>||</sup>Based on the question 'Does the child have older siblings?'

<sup>\*\*</sup>Plasma IgE against at least one of seven allergens  $\geq 0.35$  kU<sub>A</sub>/L (see Materials and Methods).

<sup>††</sup>Plasma IgE  $\geq 0.35$  kU<sub>A</sub>/L to a mix of common airborne allergens, Phadiatop™ and/or a mix of common food allergens, fx5, both (Thermo Fisher Scientific) (see Materials and Methods).

**Table 2** The association of placental inflammation with maternal sensitisation and lifestyle factors

| Test variable                                |                        | Bivariate (with lifestyle)* |      |           |       | Multivariate† |      |           |        |
|----------------------------------------------|------------------------|-----------------------------|------|-----------|-------|---------------|------|-----------|--------|
|                                              |                        | n/N                         | OR   | 95% CI    | p     | n/N           | OR   | 95% CI    | p      |
| Chorioamnionitis [any grade (1–3) versus no] | Maternal sensitisation | 114/274                     | 1.04 | 0.61–1.8  | 0.90  | 113/264       | 1.2  | 0.67–2.1  | 0.54   |
|                                              | Lifestyle‡             | 114/274                     | 1.0  |           | 0.95  |               | 1.0  |           | 0.54   |
|                                              | Partly anthroposophic  |                             | 0.94 | 0.54–1.7  | 0.84  |               | 0.71 | 0.38–1.3  | 0.28   |
|                                              | Anthroposophic         |                             | 0.90 | 0.48–1.7  | 0.75  |               | 0.80 | 0.39–1.7  | 0.56   |
|                                              | Multipara              | 113/271                     | 0.59 | 0.43–0.80 | 0.001 |               | 0.54 | 0.38–0.76 | <0.001 |
| Villitis (versus no villitis)                | Birth place home       | 114/269                     | 1.4  | 0.75–2.7  | 0.29  |               | 1.8  | 0.88–3.6  | 0.11   |
|                                              | Maternal sensitisation | 34/275                      | 2.2  | 1.1–4.7   | 0.032 | 33/265        | 2.1  | 0.95–4.6  | 0.067  |
|                                              | Lifestyle‡             | 34/275                      | 1.0  |           | 0.084 |               | 1.0  |           | 0.12   |
|                                              | Partly anthroposophic  |                             | 2.3  | 0.96–5.6  | 0.061 |               | 2.2  | 0.83–5.9  | 0.11   |
|                                              | Anthroposophic         |                             | 1.0  | 0.33–3.1  | 0.99  |               | 0.91 | 0.26–3.2  | 0.88   |
|                                              | Multipara              | 34/272                      | 0.77 | 0.49–1.2  | 0.25  |               | 0.80 | 0.49–1.3  | 0.39   |
|                                              | Birth place home       | 34/270                      | 1.3  | 0.53–3.4  | 0.53  |               | 1.4  | 0.53–3.7  | 0.50   |

\*Adjusted for lifestyle (anthroposophic, partly anthroposophic, non-anthroposophic). Presented parameter for lifestyle in the bivariate model is adjusted for maternal sensitisation.

†Variables included in the multivariate analysis: maternal sensitisation, lifestyle, parity, birth place, delivery mode, maternal age, sex of the child, living on a farm and maternal smoking during pregnancy. All in the same model.

‡Non-anthroposophic reference.

**Table 3** The association of placental inflammation with allergic sensitisation at different ages in the child

| Test variable                                |          | Bivariate (with lifestyle)* |      |          |      | Multivariate† |      |          |      |
|----------------------------------------------|----------|-----------------------------|------|----------|------|---------------|------|----------|------|
|                                              |          | n/N                         | OR   | 95% CI   | p    | n/N           | OR   | 95% CI   | p    |
| Chorioamnionitis [any grade (1–3) versus no] | 6 months | 22/193                      | 1.4  | 0.57–3.5 | 0.45 | 21/185        | 1.5  | 0.56–4.2 | 0.40 |
|                                              | 1 year   | 34/193                      | 1.7  | 0.77–3.6 | 0.19 | 33/184        | 1.4  | 0.58–3.2 | 0.48 |
|                                              | 2 years  | 40/216                      | 0.83 | 0.41–1.7 | 0.61 | 39/209        | 0.83 | 0.38–1.9 | 0.64 |
|                                              | 5 years  | 58/181                      | 0.64 | 0.33–1.2 | 0.17 | 54/174        | 0.74 | 0.36–1.5 | 0.41 |
|                                              | 6 months | 22/194                      | 1.2  | 0.31–4.5 | 0.81 | 21/186        | 1.5  | 0.37–6.3 | 0.57 |
| Villitis (versus no villitis)                | 1 year   | 34/194                      | 0.79 | 0.21–2.9 | 0.72 | 33/185        | 0.60 | 0.15–2.4 | 0.48 |
|                                              | 2 years  | 40/217                      | 1.6  | 0.58–4.3 | 0.37 | 39/210        | 1.5  | 0.53–4.5 | 0.43 |
|                                              | 5 years  | 58/182                      | 1.0  | 0.40–2.8 | 0.91 | 54/175        | 1.4  | 0.48–4.0 | 0.54 |
|                                              | 6 months | 22/194                      | 1.2  | 0.31–4.5 | 0.81 | 21/186        | 1.5  | 0.37–6.3 | 0.57 |

\*Adjusted for lifestyle (anthroposophic, partly anthroposophic, non-anthroposophic). Presented parameter for lifestyle in the bivariate model is adjusted for maternal sensitisation.

†Variables included in the multivariate analysis: maternal sensitisation, lifestyle, parity, birth place, delivery mode, maternal age, sex of the child, living on a farm, and maternal smoking during pregnancy. All in the same model.

allergens up to five years of age. Sensitisation increased over time in all children from 11% at six months of age to 32% at five years of age (Table 1). Children in the anthroposophic lifestyle group were significantly less often sensitised up to one year of age than in the other two groups (Table 1). The logistic regression models did not reveal any significant associations between placental inflammation and sensitisation up to five years of age (Table 3).

## DISCUSSION

Here we have analysed if maternal sensitisation, family lifestyle and place of birth can influence the risk for acute as well as chronic inflammation of the placenta and if these types of placental inflammation are associated with the outcome of sensitisation for the child up to five years of age.

A previous study in a prospectively collected cohort from term uncomplicated pregnancies in Stockholm (24) showed that 41% of the placentas had signs of histological chorioamnionitis; this is a high percentage, well in agreement with the present results (42%). Widely varying frequencies of histological chorioamnionitis have been recorded in the literature in term liveborns, between 5 and 68% (24). The discrepancies have been ascribed to underlying geographical or environmental factors, differences in type and selection of material or in definition of histological chorioamnionitis (reviewed in 24). Chorioamnionitis is traditionally assumed to be a proxy for ascending bacterial infection, but this notion has been challenged by work suggesting that much or most of the chorioamnionitis at term might be non-infectious, being part of a labour-induced physiological reaction (25,26). This idea could be consistent with the high frequencies of inflammation in

healthy term pregnancy, the common inability to isolate microorganisms and the discrepancy between clinical and histological picture. Haddad et al. (27) demonstrated a molecular signature of inflammation in the chorioamnionic membranes of women who had spontaneous labour even if there was no sign of histologic chorioamnionitis.

Moreover, it has been found that high-grade chorioamnionitis is over-represented in stillborn term placentas and early preterm pregnancy compared to healthy controls (24), whereas low-grade chorioamnionitis may be part of physiologic mechanism(s) in term pregnancy (28). In the present study, we find in the multivariate model an association between delivery at home and low-grade chorioamnionitis. The finding that delivery at home is a risk factor for low-grade chorioamnionitis is novel and somewhat surprising. Home delivery feasibly involves different environmental circumstances compared to hospital delivery, including the labour procedure. Lee et al. (7) have demonstrated that the risk of histological chorioamnionitis increased gradually according to the duration of labour. It could be that the total duration of labour is longer at home deliveries, but this hypothesis cannot be answered here since we do not have data on the duration of labour. Lee et al. (7) further suggested that mild placental inflammation develops during the course of labour, indicating that this type of inflammation could be largely related to the immunological/physiological environment of labour or delivery, rather than being infectious.

Strengths of the study are that the histological examination of the placentas was blinded regarding origin and all samples were evaluated by the same experienced perinatal pathologist (NP). In addition, sensitisation to allergens was estimated objectively by standardised routine methods for the presence of IgE-antibodies in blood. Further, data on delivery, including on parity, were obtained from the Swedish Medical Birth Register. A weakness is the lack of information on the duration of labour, due to its potential association with acute inflammation, which cannot be ruled out to have been longer in home than in hospital deliveries. However, rather prolonged duration should be completed at hospital and in that case diminish an introduction of systematic error. Another limitation is that lifestyle-related exposures, potentially influencing the outcome, are based on questionnaires. They were all, however, reported before delivery and thus unlikely to be a result of reversed causation in relation to the outcomes, which were all postnatally assessed.

In this study, we find a strong inverse relationship between parity and chorioamnionitis in the statistical models. This is in keeping with previous results (7) showing that nulliparity increases the odds for histologic chorioamnionitis, and is probably connected to the duration of labour. Maternal asthma has been indicated in one study as a risk factor for chorioamnionitis (6). The diagnosis of chorioamnionitis in that study was extracted from hospital databases and not verified histologically, and the definition on asthma was based on any asthma code at discharge from hospital (6). We analysed mother's allergic

sensitisation to airborne allergens, which is only partly related to adult asthma but highly related to allergic rhinoconjunctivitis (29), and observed no association with any grade of chorioamnionitis (Table 2). We found, however, a tendency for association between maternal sensitisation and villitis. Our villitis data indicate probable links between immunological imbalances in the mother and manifestation of chronic placental inflammation (villitis). This is conceivable since most villitis are believed to have immunologic background. These links, if verified, are clinically important because villitis is associated with common adverse perinatal outcomes, namely intrauterine growth restriction (9).

We hypothesised that placental inflammation could be a link for the increased risk of a child to develop allergy when the mother is allergic. We speculate that the ongoing allergic inflammation in an allergic mother increases the risk for placental inflammation. The cytokines and other inflammatory mediators produced in the inflamed placenta are also present in the amniotic fluid (30), which is in constant contact with the foetal lung. In turn, these inflammatory mediators can make the foetal lung prone to cytokine-mediated inflammation (3) and long-term respiratory disease (5) such as allergic asthma.

Previous studies have indicated an association between chorioamnionitis and doctors' diagnosed unspecified asthma or recurrent wheeze in childhood in preterm neonates (21,22), which are only to some extent related to allergy. In our present study on term pregnancies, neither chorioamnionitis nor villitis was significantly associated with sensitisation to allergens during early childhood. This is in agreement with another study on term neonates where no significant association was detected between chorioamnionitis and sensitisation at 3.5 years and seven years of age (31). The discrepant results between these studies (21,22,31), besides gestational weeks, may be explained by different definitions of childhood asthma, allergic sensitisation and chorioamnionitis.

In conclusion, our data do not support the hypothesis that the increased risk for sensitisation of a child when the mother is allergic is mediated via placental inflammation. On the other hand, our results suggest potentially important associations between maternal sensitisation and acute as well as chronic inflammation in the placenta, which must be further explored in future studies.

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## CONFLICT OF INTEREST

JA has served as a consultant on clinical trials for ALK-Abello. AS is a member in the Joint Steering Committee for the Human Translational Microbiome Program at SciLife-Lab/Karolinska Institutet together with Ferring Pharmaceuticals, Switzerland.

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