

Influence of maternal infections with viral agents or *Toxoplasma gondii* during pregnancy on fetal IgE production

Lilja G, Forsgren M, Johansson SGO, Kusoffsky E, Öman H. Influence of maternal infections with viral agents or *Toxoplasma gondii* during pregnancy on fetal IgE production.

Allergy 1997; 52: 978-984. © Munksgaard 1997.

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The importance of maternal infections with *Toxoplasma gondii*, cytomegalovirus (CMV), Parvovirus B19, respiratory syncytial virus (RSV), and influenza A and B on fetal IgE synthesis was studied in 153 pregnant women. No case of specific IgM activity or viral DNA in cord blood, indicating a congenital infection, was found. From gestational week 15 to delivery, maternal IgG-Ab seroconversion to Parvovirus B19, RSV, influenza A, or influenza B occurred in 47 women. At delivery, serologic signs of past infection with *T. gondii* were observed in 29 (19%) women, and the corresponding figure for CMV was 117 (77%). The number of women with positive IgG seroconversion during pregnancy or positive IgG-Ab activity toward the studied infectious agents at delivery did not differ significantly among infants with an increased (≥ 1.3 kU/l; $n=51$) or with an undetectable (<0.1 kU/l; $n=102$) cord-blood IgE level. These results show that genetic and other environmental factors probably have a greater influence on fetal IgE synthesis than do maternal infections during pregnancy.

Key words: atopic hypersensitivity; fetus; IgE; pregnancy; *Toxoplasma gondii*; viral infections.

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Accepted for publication 23 April 1997

There is general agreement that the frequencies of allergic and hypersensitivity reactions are increasing, especially in the industrialized parts of the world (1). The reasons for this increase in the morbidity of allergic diseases are still largely unknown, although heredity and various environmental factors are assumed to be of importance (1, 2). Allergic reactions which are due to the presence in serum of IgE antibodies (IgE-Ab) against common allergens in our environment - i.e., atopic allergy (3) - are commonest during childhood. Much interest has focused on IgE sensitization in children. It has recently been shown that T cells in cord blood (CB) respond both to food allergens (4) and to inhalant allergens (5). This has been taken as evidence of intrauterine priming of the immune system. Furthermore, the fetus is considered capable of IgE production from week 11 of gestation (6), and IgE is believed not to pass the placental barrier (7). Consequently, the presence of IgE in CB is thought to be a sign of fetal IgE synthesis (7).

The CB-IgE level has been shown to be influenced by factors such as sex, ethnicity, month of birth, maternal medication, and maternal smoking during pregnancy (8-10). However, there are few studies on the effect of maternal infections during pregnancy on fetal IgE synthesis, although infections with cytomegalovirus (CMV), herpes simplex virus, rubella virus, respiratory syncytial virus (RSV), and *Toxoplasma gondii* are all assumed to induce IgE-Ab production (11-15). On the other hand, CB-IgE levels are not influenced by maternal infections with hepatitis B during pregnancy (16), and serum levels of IgE do not differ significantly among nonpregnant adults with or without *T. gondii* infections (17). Therefore, the present study aimed to determine whether the occurrence of common viral infections - i.e., CMV, RSV, Parvovirus B19, influenza A, and influenza B - and infections with *T. gondii* during pregnancy correlated to synthesis of fetal IgE.

Material and methods

Mothers

Some 896 women having a mean age of 29 (range 17–45) years participated in the study. The women were included consecutively from 8 February to 16 June 1993, when they attended the maternity ward at Nacka Hospital in Stockholm, Sweden.

During the stay at Nacka Hospital, the participating families answered a questionnaire on the family history of allergic diseases (bronchial asthma, rhinoconjunctivitis, atopic dermatitis, urticaria, and food allergy) among first-degree relatives. The smoking habits of the fathers and the pregnant women were also recorded.

Sampling of maternal blood

A maternal serum sample, taken at gestational weeks 12–15, was obtained from the department of virology of Huddinge Hospital, Stockholm. In the Stockholm area, all pregnant women at this gestational age are tested for immunity to rubella. At delivery, a venous blood sample was taken from each woman. All sera were stored at -20°C , pending analysis.

Infants

Some 901 infants were born, including five pairs of twins. There were 450 girls and 451 boys; all infants were full-term.

Sampling of cord blood (CB)

Cord blood (CB) from the umbilical vein was obtained by needle aspiration from all neonates. Aspiration was used to reduce the risk of maternal contamination of CB (18). Serum was separated and stored at -20°C , pending analysis.

Immunoglobulin determinations

IgA. The serum concentration of IgA (mg/l) was determined by sandwich ELISA, as described previously (19). The upper normal limit of the CB-IgA level was set at 14 mg/l, calculated as the geometric mean plus three standard deviations (SD) in 20 neonates with maternal atopic heredity and CB-IgE <0.1 kU/l (19). An IgA value above 14 mg/l was taken as an indication of possible contamination of CB with maternal blood.

IgE. The IgE level (kU/l) in CB was analyzed in single samples with CAP-FEIA, modified by an extended standard curve but otherwise in accordance with the recommendations of the manufacturer

(Pharmacia Diagnostics, Uppsala, Sweden). The lower detection limit of the test was 0.1 kU/l. CB-IgE levels exceeding 1.3 kU/l ($\geq$ geometric mean plus 2 SD) (20) were analyzed in duplicate.

IgG antibodies to viruses. Maternal sera, in dilution 1/100, were analyzed for Parvovirus B19 IgG-Ab activity against recombinant antigen (Dakopatts, Copenhagen, Denmark), according to the instructions of the manufacturer, and by the anti-immunoglobulin ELISA technique for IgG-Ab activity against RSV (21), influenza A H1N1 and H3N2, and B virion antigens (22). A net absorbance value ≥ 0.2 , exceeding 3 SD of repeated titrations, was considered a positive reaction, and a difference between paired sera of this magnitude was thought to indicate a significant rise in antibodies.

IgG-Ab activity against CMV (nuclei extract antigen) and against *T. gondii* was analyzed by the anti-immunoglobulin ELISA technique (23) and by direct agglutination (BioMerieux, Paris, France), respectively. A positive reaction at serum dilution 1/100 (CMV) and $>1/20$ (*T. gondii*) was taken as an indication of past infection.

IgM antibodies to viruses

CB was assayed for IgM activity against CMV (enzyme-labeled nuclei extract antigen) (24), against Parvovirus B19 by the μ -capture ELISA technique (Dakopatts, Copenhagen, Denmark), and against *T. gondii* by the μ -capture immunosorbent technique (ISAGA, BioMerieux, Paris, France). A positive result, according to the criteria of the assay, was considered to indicate viral-specific IgM activity. The serum dilution was 1/20.

Polymerase chain reaction (PCR)

Parvovirus B19 DNA was assayed in serum by the nested PCR technique with primers in the *VPI* gene (25).

Study design

High and low CB-IgE groups. The infants were divided into two subgroups according to the results of the CB-IgE determinations: *high CB-IgE group* – infants with CB-IgE levels ≥ 1.3 kU/l; *low CB-IgE group* – infants with no detectable IgE in CB, i.e., CB-IgE <0.1 kU/l. For each infant in the high CB-IgE group, two “control” infants with no detectable IgE levels were selected from the same cohort. The selection was stratified according to sex, but was otherwise performed at random. The selected CB samples in the high and low CB-IgE

groups were checked for maternal contamination by determination of CB-IgA.

Serologic signs of maternal infection with the selected viral agents and *T. gondii*. The IgG-Ab activities against influenza A and B, RSV, and human Parvovirus B19 at gestational weeks 12–15 and at delivery were simultaneously determined in serum samples from the mothers of the children in the high and low CB-IgE groups (Table 1). The number of women with serologic signs of IgG-Ab seroconversion or a significant IgG-Ab rise was determined.

The IgG-Ab activities against CMV and *T. gondii* were screen-tested in the selected maternal sera sampled at delivery (Table 1). Positive titers – i.e., CMV $\geq 1/100$ and *T. gondii* $\geq 1/20$ – were taken as an indication of past infection.

Serologic signs of fetal infection with Parvovirus B19, *T. gondii*, and CMV. IgM-Ab activities in CB against Parvovirus B19, CMV and *T. gondii*, indicating congenital infection, were studied (Table 1). CB IgM-Ab levels against CMV and *T. gondii* were analyzed only if the corresponding maternal serum sample showed positive IgG-Ab activities at delivery (CMV $\geq 1/100$; *T. gondii* $\geq 1/20$). CB IgM-Ab levels against Parvovirus B19 were analyzed in 15 infants, randomly selected from among those whose mothers had an IgG-Ab level $>1/100$ at delivery (Table 1).

Presence of Parvovirus B19 DNA in CB. Children of mothers with verified (IgG-Ab seroconversion) Parvovirus B19 infection during pregnancy were tested for Parvovirus B19 DNA in CB with PCR.

Ethics

The study was approved by the ethics committee at Södersjukhuset, Stockholm, Sweden. Informed consent was given by the parents before the subject entered the study.

Statistical analysis

The chi-square test or, in the case of small expected frequencies, Fisher's exact test was used to evaluate hypotheses of variables in contingency tables. A *P* value (two-tailed) < 0.05 was considered significant.

Results

High and low CB-IgE groups

Fifty-one infants (6%) (33 boys and 18 girls) had a CB-IgE level ≥ 1.3 kU/l and were placed in the high CB-IgE group (Table 2). Among 245 (27%) infants with undetectable CB-IgE levels (i.e., CB-IgE < 0.1 kU/l), 102 infants (66 boys and 36 girls) were randomly selected. These infants were placed in the low CB-IgE group. Both groups were comparable with regard to smoking habits of the parents (Table 2) and gestational age. However, maternal atopic heredity was significantly ($P < 0.01$, chi-square) more frequent among the infants in the high CB-IgE group, and there were significantly ($P < 0.05$) more atopic siblings in the same group of infants. Besides, significantly ($P < 0.01$, chi-square) more infants in the high CB-IgE group were born in February–April than April–June, as compared to the infants in the low CB-IgE group (Table 2).

Serologic signs of maternal IgG-Ab seroconversion to RSV, Parvovirus B19, and influenza A and B between gestational weeks 12–15 and delivery

The numbers of paired maternal serum samples available for analyses were 47 and 99 in the high CB-IgE group and low CB-IgE group, respectively (Table 3).

The number of women with IgG-Ab seroconversion and/or the number of women with significant rises in IgG-Ab levels against the selected viral agents during the observation period are presented in Table 3. In two women belonging to the low CB-IgE group, IgG seroconversion against RSV was detected, indicating infection with RSV during pregnancy. Four women had infection with Parvovirus B19, one in the high CB-IgE group and three in the low CB-IgE group. Two women in each group had IgG-seroconversion against influenza A.

Table 1 Study design. Determination of IgG-Ab levels of antibody activities in maternal serum samples from gestational weeks 12–15 and delivery and IgM-Ab levels in CB samples against *T. gondii* and selected viral agents

	Maternal IgG-Ab analysis		Infant IgM-Ab analysis Cord blood
	Gest. weeks 12–15	Delivery	
Congenital infections			
<i>T. gondii</i>	ND	A	A*
CMV	ND	A	A*
Parvovirus B19	A	A	A**†
Other maternal viral infections			
RSV	A	A	ND
Influenza A	A	A	ND
Influenza B	A	A	ND

A -- analysis done; ND -- analysis not done; * analysis was done if mother had IgG Ab against *T. gondii* ($n = 29$) or against CMV ($n = 117$) at delivery; ** analysis was done on 15 CB samples from infants with Parvovirus B19-positive mothers; † PCR analysis was done in samples from children of four mothers with serologic signs of Parvovirus infection during pregnancy.

Table 2. Demographic data of infants in high and low CB-IgE groups

	High CB-IgE	Low CB-IgE
CB-IgE (kU/l)	≥1.3	<0.1
n	51	102
Sex M/F (n)	33/18	66/36
Date of birth (%)		
8 Feb-15 April	54**	31
16 April-15 June	46	69**
Atopic heredity (%)		
Maternal	61**	35
Paternal	41	39
Siblings	41*	26
Smokers (%)		
Mother	20	19
Father	16	16

P* < 0.05; *P* < 0.01 (chi-square analysis).

Interestingly, there were 30 women, nine in the high CB-IgE group and 21 in the low CB-IgE group, with serologic signs of infection with influenza B during pregnancy. The number of pregnant women showing serologic evidence of infection with these viruses was about the same in the two study groups (chi-square analysis or Fisher's exact test).

Maternal IgG-Ab activity in serum at delivery and fetal IgM-Ab activity in CB against T. gondii and various viral agents

Twenty-nine women were IgG seropositive against *T. gondii* (Table 4). Nine belonged to the high CB-IgE group and 20 to the low CB-IgE group (NS = not significant, chi-square analysis). None of the corresponding 29 CB samples had IgM-Ab activity against *T. gondii*.

Almost all the selected women were seropositive to RSV and influenza A and B at delivery (Table 4), indicating that these viral infections are widespread in the community. In contrast, only 117 women, 42 in the high CB-IgE group and 75 in the low CB-IgE group, were seropositive to CMV at delivery (NS, chi-square analysis). No case of IgM-anti-CMV in CB was demonstrable. Ninety-

Table 3. Number of women with IgG seroconversion against Parvovirus B19, RSV, and influenza A and B between gestational weeks 12-15 and delivery in relation to number of women tested

	High CB-IgE	Low CB-IgE	P§
Parvovirus B19	1/47	3/99	NS
RSV	0/47	2/99	NS
Influenza A	2/47	2/99	NS
Influenza B	9/47	21/99	NS

§ Fisher's exact test and chi-square analysis; NS = not significant.

two women, 26 in the high CB-IgE group and 66 in the low CB-IgE group were seropositive to Parvovirus B19 (NS, chi-square analysis), but among 15 infants, selected at random among those whose mothers had a positive IgG-Ab test against Parvovirus B19, the corresponding CB-IgM test was negative.

DNA Parvovirus B19 determined by PCR

There were four women with IgG seroconversion to Parvovirus B19, indicating maternal infection during pregnancy. However, the PCR test for Parvovirus B19 DNA in the corresponding CB samples was negative.

Maternal contamination of CB samples

All results so far presented were obtained without taking into consideration possible maternal contamination of CB. For this reason, all data were reevaluated on the basis of the CB-IgA results, where a CB-IgA level > 14 mg/l was regarded as possible maternal contamination. In the low CB-IgE group, there were no samples with signs of contamination. However, in the high CB-IgE group, four (8%) CB samples had elevated CB-IgA. Exclusion of these sera did not alter the significance of the results (data not shown).

Influence of a positive history of atopic disease among first-degree relatives

When neonates without atopic heredity among first-degree relatives were excluded, 40 (78%) and

Table 4. Presence (positive) and absence (negative) of maternal IgG-Ab levels at delivery and fetal IgM-Ab levels in CB against *T. gondii* and various viruses in relation to high and low CB-IgE levels

Tested agent	CB-IgE	Mother IgG Ab		Neonate IgM Ab	
		pos	neg	pos	neg
<i>T. gondii</i>	High	9	42	0	9
	Low	20	82	0	20
CMV	High	42	9	0	42
	Low	75	27	0	75
Parvovirus	High	26	25	0	6
	Low	66	36	0	9
RSV	High	50	1	ND	ND
	Low	101	1	ND	ND
Influenza A	High	51	0	ND	ND
	Low	101	1	ND	ND
Influenza B	High	51	0	ND	ND
	Low	100	2	ND	ND

No significant group differences were found [Fisher's exact test and chi-square analysis]. ND = analysis not done.

68 (67%) infants were left in the high and low CB-IgE groups, respectively. However, including only infants with a positive family history of atopic disease did not significantly change the distribution of infections with the various viral agents or *T. gondii* between study groups (data not shown).

Discussion

In this study, no correlation was found between the CB-IgE levels and maternal infections during pregnancy with various viral agents and *T. gondii*. This is of interest, since the level of total IgE in serum has been shown to be elevated during the acute phase of some viral infections (26, 27). Furthermore, infections with CMV, herpes simplex, rubella, RSV, and *T. gondii* are usually associated with the synthesis of antigen-specific IgE (11–15). However, during the convalescent phase of a viral infection, the total IgE level usually falls (26, 27), and the assumed virus-specific IgE seems to disappear more rapidly from the circulation than the corresponding virus-specific IgD and IgG antibodies (13). Thus, the determination of the CB-IgE level may be influenced by a time factor, and viral infections early in pregnancy may lead to a renormalized CB-IgE.

The absence of correlation between maternal infections during pregnancy and fetal IgE responses is in line with earlier observations. Thus, a lower incidence of elevated CB-IgE levels in neonates of hepatitis B-positive mothers than in neonates of hepatitis B-negative mothers has been reported (16). Moreover, the group of infants with prematurely ruptured membranes, a condition where the fetus is subject to transmission of maternal infection, has not been associated with elevated CB-IgE levels (28). Furthermore, rubella-specific CB-IgE was detected in only one of 12 CB sera from neonates with congenital rubella (13). Our results refute those of a Russian study which found maternal infections with herpes simplex virus to stimulate fetal IgE synthesis (29). However, there is evidence that stressful events *in utero* can cause alterations in lymphocyte function in the fetus, including lymphocytes bearing the IgE-Fc receptor (30). It has also been shown that T cells from hepatitis B carriers during a viral infection can produce a soluble factor that suppresses antibody synthesis (31). It is speculated that such a maternal, low-molecular-weight, soluble factor via placental transfer may induce fetal T-cell suppression of IgE-production *in utero* (16). Furthermore, viral infections usually stimulate TH1-cells to synthesize interferon-gamma and may, at the same time, have an inhibitory effect on TH2-induced IgE synthesis (32).

Rubella, *T. gondii*, Parvovirus B19, and herpes-virus agents – e.g., CMV, Epstein-Barr virus (EBV), and herpes simplex virus (HSV) – are all known to cause congenital infections (33). Most pregnant women in Sweden have either had a rubella infection during childhood or adolescence or have been vaccinated. Thus, rubella virus no longer circulates in this community, and that is why no congenital infection with rubella has been diagnosed in the Stockholm area since 1985 (rubella surveillance data; Swedish Institute for Infectious Disease Control). Almost all fertile women have been infected with EBV, and ~70–75% of them with HSV (33–35). Seroconversions during pregnancy are rare (Forsgren, unpublished data). Consequently, it seems unlikely that maternal infections with rubella, EBV, and HSV, with or without a congenital infection, would occur in our test population. For this reason, we did not determine antibody levels against these viral agents in the present investigation.

In this study, no child had serologic signs of congenital infection with *T. gondii* (IgM) or CMV in assays with diagnostic sensitivity of $\geq 80\%$ (24). The prevalence of congenital infections with *T. gondii* outside Scandinavia, as well as in Finland and in Norway, has been reported to be 0.1% (36). The rate of congenital infections with CMV varies between 0.4 and 2.4% (36, 37). In a previous study in Sweden, the number of congenital infections with CMV was 0.5% (38). Furthermore, infections with *T. gondii* and CMV show no seasonal variations (34). Therefore, the prevalence of congenital infections with *T. gondii* and CMV in this study – i.e., no case observed – corresponds to what would be expected in a random sample of this size of pregnant women.

Although no infant had congenital CMV infection, 77% of the women were seropositive, i.e., had demonstrable IgG-Ab against CMV at delivery (Table 4). The corresponding IgG seroprevalence to *T. gondii* was 19% (Table 4). These figures agree with earlier Swedish studies (38, 39). We also found that women who were seropositive for CMV and/or *T. gondii* were equally distributed between mothers of infants in the low and high CB-IgE groups.

Parvovirus B19 can cross the placenta to the fetus, and a congenital infection often manifests itself by hydrops fetalis and severe anemia in the neonate (40). Whether a congenital infection with Parvovirus B19 is always associated with IgM seroconversion in the fetus is debatable (41). On the other hand, the identification of virus-specific DNA with PCR has high sensitivity and specificity (25). The annual seroconversion of Parvovirus B19 infections in women of childbearing age has been

reported to be 1.5% (42); in pregnant women, the infection spreads to the fetus in around 30% (41). However, we were unable to identify a congenital infection with Parvovirus B19 although we used both IgM in CB (in a randomly selected group of infants) and PCR technology (in four infants whose mothers had IgG seroconversion to Parvovirus B19). This also indicates that congenital infections with Parvovirus B19 are probably not associated with fetal IgE synthesis.

The importance of infections with influenza A and B in atopic diseases has been emphasized (43), and IgE-mediated histamine release from human basophils by viruses – i.e., influenza A – has been described by Ida et al. (44). The number of seroconversions to influenza B (Table 3) in the present study indicates that during February to June 1993, there was an epidemic of influenza B in the Stockholm area. This was verified by epidemiologic data from the medical authorities in Stockholm (45). The same epidemiologic data showed that the period chosen for the study was characterized by a high prevalence of infections with influenza A and RSV in the community. This strengthened the view that the period selected during 1993 was the right one. Furthermore, the reported infections were evenly distributed from January to June 1993 (45). Thus, the observed difference in time of birth among the infants in the high and low CB-IgE groups has probably not had any major influence on the results in our study.

During recent years, much interest has focused on RSV infections and the development of bronchial asthma during childhood (46). Such infections are widespread in the population. Thus, it was not surprising that almost all the women were seropositive (IgG) at delivery (Table 4), indicating previous infection with RSV. Two women had serologic signs of RSV infection during pregnancy, but their infants were born with CB-IgE levels below 0.1 kU/L.

The number of infants with elevated CB-IgE levels in the present study was similar to that in previous studies (8, 20). Possible maternal contamination of CB as an explanation of elevated CB-IgE levels is currently under debate (8, 18, 19, 47). Some authors have proposed that elevated IgA levels in CB are of value in assessing maternal contamination of CB (8). However, results from our group indicate that this is doubtful (47). Consideration of possible maternal contamination of CB did not change the results of the study in any significant way. Furthermore, the conclusions of the study were the same even when infants with a family history of atopic disease were included.

In summary, maternal infections with *T. gondii*, CMV, RSV, influenza A, influenza B, and Parvovirus B19, with or without spread of the infection to the fetus, seem not to be correlated to CB-IgE levels or to fetal IgE synthesis. Genetic and/or environmental factors, other than infections during pregnancy, are probably of greater importance for inducing IgE synthesis *in utero*.

Acknowledgments

The advice about statistics given by Per Näsman, BA, Department of Statistics, University of Stockholm, and the technical assistance of Hikka Härmää at the Department of Virology, Huddinge Hospital, Stockholm, and of Monica Nordlund at the Department of Clinical Immunology, Karolinska Hospital, Stockholm, are gratefully acknowledged. The study was supported by the Swedish Medical Research Council (grant no. 16X-105), the Swedish Medical Association, the National Association for the Prevention of Asthma and Allergy (RmA), the Samaritan Foundation, the Södersjukhuset, the Karolinska Institute, and the Vårdal Foundation.

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