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Febrile and gynecological infections during pregnancy are associated with a greater risk of childhood eczema

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Abstract

Background: Mounting evidence suggests that fetal exposures may exert long-term effects on the function of the skin and of the immune system. This study aimed at assessing whether maternal complications during pregnancy are associated with an increased risk of eczema during childhood.
Methods: The associations between hypertension/preeclampsia, febrile infections, or gynecological infections during pregnancy and the occurrence of childhood eczema were studied in a population (n = 3907) of children, aged 3–14 yrs, living in Italy. Their parents filled in a standardized questionnaire about the presence of children's eczema and the events that occurred during pregnancy, birth, and the first year of the child's life.
Results: 7.7%, 3.8%, and 6.1% of the pregnancies were complicated by hypertension/preeclampsia, febrile infections, and gynecological infections, respectively. The prevalence of eczema was significantly higher in children born to mothers who had experienced febrile (35.5% vs. 22.0%; $p < 0.001$) or gynecological infections (35.3% vs. 21.6%; $p < 0.001$) compared with those born to mothers who had not suffered from that specific pregnancy complication, while hypertension/preeclampsia was not significantly associated with childhood eczema. After adjusting for potential confounders, the risk of eczema was significantly higher in children born to mothers who reported febrile infections during the 1st trimester (OR: 2.32; 95%CI: 1.11–4.82) and gynecological infections during the 3rd trimester of pregnancy (OR: 2.73; 95%CI:1.73–4.31).
Conclusions: Fetal exposure to febrile and gynecological infections might enhance the risk of eczema in the offspring, especially when occurring in specific trimesters of pregnancy. These findings suggest that febrile and gynecological infections might interfere with fetal and perinatal programming of the immune function and skin through different mechanisms.

Eczema is a chronic inflammatory disease of the skin, which is characterized by epidermal dryness and itchiness that causes typical relapsing lesions and plaques. Eczema is the most common chronic disease in infancy, and its prevalence has been dramatically on the increase during the last 3 decades (1). Despite the high prevalence and the important socio-economical issues related to the disease, eczema still has a far-to-be-understood etiology, in which complex interactions between genetic, immunological, and environmental factors play a critical role.

Emerging evidence from epidemiological and animal studies suggests that fetal programming is a very delicate stage for the development of the immune and neuro-endocrine systems and that prenatal exposures to physical and psychological stressors may induce epigenetic and immunologic modifications that may result in phenotype alterations in childhood (2–4). However, only few epidemiological studies have so far investigated the effects of prenatal exposures on the development of skin disorders (5–8).

Hypertension and preeclampsia, febrile infections, and gynecological infections are some of the most common complications that may occur during pregnancy. They have been associated with high risks of adverse birth outcomes, such as pre-term delivery and low birth weight, as well as with a high risk of cesarean sections (9, 10).

To date, there is inconsistent evidence to support if – and to what extent – pregnancy complications affect the susceptibility

Abbreviations
CI, confidence interval; OR, odds ratio.

of children to develop eczema. The objective of this study is to assess whether maternal hypertension/preeclampsia, febrile infections, and gynecological infections during pregnancy are associated with an increased risk of eczema during childhood, and whether the specific pregnancy trimester when the complication occurred is critical.

Methods

Study design and participants

The association between *in utero* exposures and eczema in the offspring was investigated using the data collected in the Viadana study (11). This was a cross-sectional survey performed in December 2006 and aimed at investigating the health of the children living in the industrial district of Viadana. All the children (n = 3907) aged 3–14 and enrolled in the school registers of the district were included in this survey. Parents were asked to fill in a detailed questionnaire on their children's health and on potential prenatal, postnatal, and current risk factors for atopic disorders. The local ethics committee approved the study protocol.

The Viadana questionnaire

The Viadana questionnaire (freely available at: http://biometria.univr.it/viadanastudy) investigated the presence of atopic disorders, including eczema, in children. Most of the questions were taken from the International Study of Asthma and Allergies in Childhood (ISAAC) and the Italian Study on Respiratory Disorders in Childhood and the Environment (SIDRIA-2) standardized questions, which had been validated in previous international surveys (12, 13).

A child was considered to have had eczema in case of an affirmative answer to the following question: "Has your child had an itchy rash on one or more parts of the skin, which was coming and going for at least 6 months, at any time in the past?" (13). The main analyses were also repeated using an alternative definition based on parental-reported diagnosis (affirmative answer to the question: "Has your child ever had eczema?").

The questionnaire collected information about the following complications in pregnancy and the trimester in which they occurred: (i) hypertension for which the mother had to take medicines or preeclampsia; (ii) episodes of fever due to infections; (iii) gynecological infection for which the mother had to take medicines.

Other covariates

Information about the characteristics of the children and of their families (gender, age of the child and nationality, parental school education level as proxy of socio-economical status, parental smoking, familiar history of asthma, familiar history of eczema, person who filled in the questionnaire) and on environmental exposure factors (residential area, heavy traffic level, exposure to industrial sources of air pollutants, pets, number of older siblings, early-life exposures to farm animals, to damp spots, molds or mildew on the walls of the child's bedroom, sharing the bedroom with an older sibling) was also collected (Table 1).

Moreover, the following pregnancy, birth and perinatal characteristics were considered in the analyses (Table 2): maternal smoking during pregnancy, mother's age at delivery, gestational time, vaginal/cesarean delivery, weight at delivery, mother's experience of stressful life events (mourning, loss of her job or her husband's job, separation), use of medicines during pregnancy (acetaminophen/paracetamol, antibiotics, cortisone or cortisone-like medicines, anti-asthma drugs), duration of breastfeeding, use of antibiotics in the first year of the child's life.

Statistical analyses

The distribution of categorical variables was described with percentages, and the differences between groups were tested by chi-squared tests. The associations between pregnancy complications and childhood eczema were evaluated using multiple logistic regression models. Each pregnancy complication was evaluated both as a 2-level variable (0 = absent, 1 = present) and as a 5-level variable considering the trimester when the complication occurred (0 = absent, 1 = first trimester, 2 = second trimester, 3 = third trimester, 4 = any two or three pregnancy trimesters). Child's gender and age were considered as adjustment variables in all the models. Three alternative sets of adjustment variables were considered for each pregnancy complication: (i) The first model was adjusted for the characteristics of the child/ family and for environmental factors (only variables associated with eczema prevalence at the 10% level, see Table 1); (ii) the second model was further adjusted for pregnancy, birth, and perinatal characteristics (only variables associated with eczema prevalence at the 10% level, see Table 2); (iii) in the final model, hypertension/preeclampsia, febrile infections, and gynecological infections were added together in the same model in addition to all the previous factors and mutually adjusted.

Statistical analyses were performed with STATA 12.1 (Stata Corp. College Station, TX, USA).

Results

The questionnaires were given to 3907 children at school for their families, and 3854 questionnaires were filled in and returned (response rate 98.6%). A total of 3794 children, for whom complete information about occurrence of eczema was available, were included in the study. A total of 842 of them (22.2%; 95%CI: 20.9–23.5%) were reported to have had eczema at some time in the past.

Factors associated with the prevalence of eczema in children

Highly educated, Italian parents with a history of eczema reported more frequently that their children had eczema than disease-free, less educated, and foreign parents (Table 1) ($p < 0.01$). Mothers were also significantly more likely to report eczema than fathers or other caregivers.

Table 1 Distribution of children's characteristics and environmental exposure factors and their associations with the prevalence of childhood eczema

Variable		n	Prevalence of eczema (%)	p-value*
Gender	Male	2049	23.0	0.273
	Female	1765	21.4	
Age	Below 6 yrs	1001	22.9	0.389
	6–10 yrs	1382	23.0	
	Above 10 yrs	1428	21.1	
Familiar history of eczema	No	2828	19.3	<0.001
	Yes	747	33.2	
Familiar history of asthma	No	3212	20.7	<0.001
	Yes	380	32.6	
Parental smoking	No	1520	22.0	0.624
	Yes	2103	22.7	
Nationality	Italian	3477	23.5	<0.001
	Foreign	294	8.5	
Parental education	Lower education	1334	19.3	0.003
	Secondary school	1889	24.3	
	University	525	23.8	
Person who filled in the questionnaire	Mother/Both parents	3551	23.0	<0.001
	Father/Other	203	10.0	
Residential area	Countryside	1913	22.9	0.229
	Urban	1602	21.0	
	Industrial area	218	25.2	
Traffic level near home	High	352	22.7	0.837
	Low	3421	22.2	
Exposure to industrial pollution†	Low	1355	21.0	0.445
	Intermediate	970	22.8	
	High	1448	22.9	
Ever kept a dog	Yes	749	24.0	0.156
	No	2397	21.6	
Ever kept a cat	Yes	701	24.3	0.160
	No	2342	21.7	
Older siblings	Yes	1587	21.6	0.523
	No	2235	22.5	
Sharing bedroom with older siblings‡	Yes	973	21.8	0.603
	No	2757	22.6	
Exposure to farm animals‡	Yes	458	23.8	0.453
	No	3265	22.2	
Mold or damp in child's bedroom‡	Yes	568	29.9	<0.001
	No	2915	21.0	

*chi-squared test.
†As described in de Marco et al.(15).
‡During the first year of children's life.

Presence of damp spots, mold, or mildew on the walls or ceiling of the child's bedroom during the first year of the his/her life was significantly associated with a greater risk of eczema in childhood.

Table 2 shows the association between pregnancy, birth, and perinatal characteristics and eczema in the child. Children born to mothers who had experienced stressful life events during pregnancy had a significantly higher prevalence of eczema compared with non-exposed children. Mothers who had used paracetamol or cortisone during pregnancy and mothers with a younger age at delivery were significantly more likely to report eczema in their children. Children treated with two or more cycles of antibiotics in the first year of their life were also at a greater risk of having eczema.

Table 2 Distribution of pregnancy, birth, and perinatal characteristics and their associations with the prevalence of childhood eczema in the offspring

Variable		n	Prevalence of eczema (%)	p-value*
Maternal smoking†	No	3463	22.1	0.357
	Yes	285	24.5	
Stressful life events†	No	3387	21.6	<0.001
	Yes	332	31.9	
Use of paracetamol†	No	2538	20.2	<0.001
	Yes	1062	28.1	
Use of antibiotics†	No	3420	21.9	0.056
	Yes	263	27.0	
Use of cortisone†	No	3562	22.1	0.003
	Yes	88	35.2	
Anti-asthma drugs†	No	3645	22.3	0.850
	Yes	52	21.2	
Maternal age at delivery	<21 yrs	307	13.6	<0.001
	21–35 yrs	3074	23.3	
	>35 yrs	381	20.5	
Type of delivery	Vaginal	2641	22.7	0.351
	C-section	1141	21.3	
Term of delivery	Preterm	2997	19.8	0.138
	Regular	334	23.6	
	Late term	237	19.7	
Birth weight	<2500 g	277	20.0	0.417
	2500–4200 g	3305	22.7	
	>4200 g	128	20.3	
Breastfeeding	<1 month	1136	22.6	0.796
	≥1 month	2563	22.2	
Antibiotics‡	Never	1936	20.0	<0.001
	1 cycle	1235	23.4	
	≥2 cycles	535	28.9	

*chi-squared test.
†During pregnancy.
‡During the first year of children's life.

Associations between complications in pregnancy and risk of childhood eczema

285 (7.7%), 141 (3.8%), and 223 (6.1%) pregnancies were reported to have been complicated by hypertension/preeclampsia, febrile infections, and gynecological infections, respectively. The prevalence of eczema was significantly higher in children born to mothers who had experienced febrile (35.5% vs. 22.0%) or gynecological infections (35.3% vs. 21.6%) compared with those born to mothers who had not suffered from that pregnancy complication (Fig. 1), while hypertension/

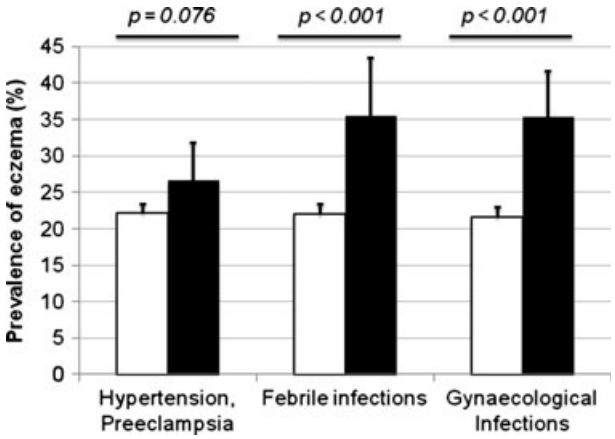

Figure 1 Prevalence (with 95% CI) of eczema in children born to mothers who did (black columns) and did not report (white columns) complications during pregnancy.

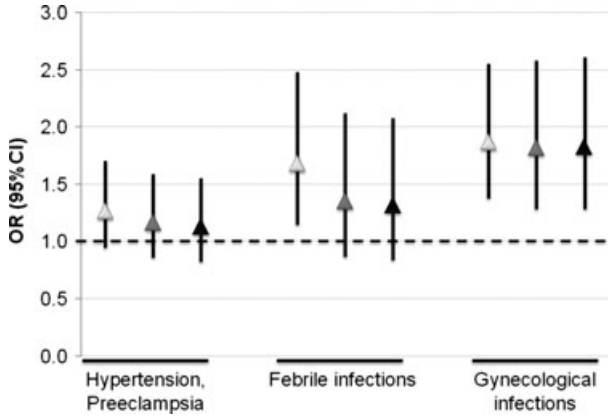

Figure 2 Risk of eczema (OR with 95%CI) in children born to mothers who reported complications during pregnancy (compared with children born to mothers who did not). In the first model (white Δ), the risks were adjusted for sex, age, familiar history of eczema and of asthma, nationality, parental education, person who filled in the questionnaire, maternal age at delivery, presence of mold or damp in the bedroom during the first year of life; in the second model (gray ▲) the risks were adjusted for previous factors plus maternal stressful life events in pregnancy, maternal use of drugs (paracetamol, antibiotics, and cortisone) during pregnancy, duration of breastfeeding, use of antibiotics during the first year of life; in the final model (black ▲), the risks were adjusted for all the factors above and mutually adjusted for the other pregnancy complications.

preeclampsia was not significantly associated with childhood eczema (p = 0.076). Only the occurrence of gynecological infections, however, was still significantly associated with childhood eczema after adjustment for potential confounders and mutual adjustment for the other pregnancy complications (OR = 1.82, 95%CI: 1.28–2.61) (Fig. 2).

Association between complications at specific trimester of pregnancy and risk of childhood eczema

Table 3 shows the associations between reported complications at specific pregnancy trimesters and childhood eczema. After adjusting for all the other covariates, the risk of eczema was significantly higher in children born to mothers who reported febrile infections in the first trimester (OR = 2.32, 95%CI: 1.11–4.82) or who reported gynecological infections in the third trimester (OR = 2.73, 95%CI: 1.73–4.31), while we did not find significant associations when those pregnancy complications were reported in any other trimester. These results were confirmed when using parental-reported diagnosis of eczema as an alternative outcome (Table S1 in the online data supplement).

Discussion

There is increasing evidence that the natural history of atopic disorders begins in prenatal life. The fetal stage is the most critical period in developmental programming, and perturbations of the physiological *in utero* environment may induce epigenetic and immunologic alterations with potential health consequences for later life (3).

In this study, we showed that children born to mothers who reported to have had febrile and gynecological infections during pregnancy were more likely to have eczema in childhood, especially when these were reported to have happened during the 1st and 3rd pregnancy trimester, respectively. These associations were also observed when the main potential confounders were considered in the analyses. Factors included socio-demographic factors (nationality, parental school education), family history of atopic disorders, maternal age at delivery, fetal or early-life exposure to medicines, maternal stressful life events, and allergens (3, 8, 14–17).

Hypertension or preeclampsia and childhood eczema

Hypertension and preeclampsia are major pregnancy complications affecting maternal and fetal health. In our sample, 285 pregnancies (7.7%) were reported to have been complicated by hypertension or preeclampsia. Previous research showed that maternal hypertension and preeclampsia were associated with an increased risk of wheezing and of atopic sensitization among offspring (14, 18). In our sample, however, we did not find a significant association between hypertension/preeclampsia and the risk of childhood eczema after adjusting for all potential confounders.

Febrile infections and childhood eczema

3.8% of pregnancies were reported to have been complicated by febrile infections in our sample. In agreement with the previous studies, we found that children exposed to maternal febrile infections were at higher risk for eczema development (3, 5). In particular, we found that the risk was more than doubled when these febrile episodes occurred during the first trimester of gestation. A similar association had also been

Table 3 Prevalence of childhood eczema in children born to mothers who did and did not suffer from pregnancy complications, stratified by timing of exposure, and odds ratios (OR) with 95%CI for the associations between pregnancy complication and eczema prevalence

	n	Prevalence of eczema (%)	Adjusted† OR (95%CI)	Adjusted‡ OR (95%CI)	Mutually adjusted§ OR (95%CI)
Hypertension or Preeclampsia					
No	3395	22.1	1	1	1
1st trimester	19	10.5	0.51 (0.11–2.27)	0.30 (0.04–2.37)	0.32 (0.04–2.49)
2nd trimester	36	13.9	0.61 (0.23–1.61)	0.56 (0.20–1.54)	0.56 (0.20–1.56)
3rd trimester	172	27.9	1.26 (0.87–1.82)	1.24 (0.84–1.81)	1.23 (0.83–1.82)
Any 2 or 3 trimesters	46	37.0*	**2.16 (1.14–4.13)**	1.59 (0.80–3.16)	1.42 (0.68–2.98)
Febrile Infections					
No	3495	22.0	1	1	1
1st trimester	40	47.5***	**2.52 (1.26–5.01)**	**2.25 (1.09–4.62)**	**2.32 (1.11–4.82)**
2nd trimester	45	35.6*	1.76 (0.93–3.34)	1.35 (0.65–2.79)	1.26 (0.59–2.70)
3rd trimester	34	23.5	0.91 (0.36–2.28)	0.80 (0.29–2.22)	0.74 (0.26–2.09)
Any 2 or 3 trimesters	10	50.0*	2.81 (0.78–10.1)	1.81 (0.36–9.22)	1.63 (0.28–9.34)
Gynecological Infections					
No	3407	21.6	1	1	1
1st trimester	29	27.6	1.24 (0.48–3.22)	1.03 (0.36–2.95)	0.99 (0.34–2.89)
2nd trimester	43	27.9	1.18 (0.58–2.42)	1.04 (0.48–2.29)	0.92 (0.39–2.22)
3rd trimester	112	41.1***	**2.52 (1.72–3.71)**	**2.53 (1.61–3.95)**	**2.73 (1.73–4.31)**
Any 2 or 3 trimesters	25	36.0	2.04 (0.90–4.63)	2.08 (0.82–5.28)	1.85 (0.67–5.08)

*$p < 0.05$; ***$p < 0.001$ with respect to the reference category (no pregnancy complication).
†Adjusted for sex, age, familiar history of eczema and of asthma, nationality, parental schooling, person who filled in the questionnaire, maternal age at delivery, presence of mold or damp in the bedroom during the first year of life.
‡Adjusted for factors in † plus maternal stressful life events in pregnancy, maternal use of drugs (paracetamol, antibiotics, and cortisone) during pregnancy, duration of breastfeeding, use of antibiotics during the first year of life.
§Adjusted for all the factors in † and ‡, plus mutually adjusted for the other pregnancy complications.
Statistically significant associations are shown in bold.

previously observed by Xu and colleagues in a large cohort of children aged seven (5). Antibiotics and paracetamol are the most commonly used drugs for treating febrile infections in pregnancy. Fetal exposure to paracetamol has been associated with a greater risk to develop allergic diseases in childhood (19), and previous studies have also reported that use of antibiotics during pregnancy increases the risk of eczema (3), although there is conflicting evidence on this association (20). As we accounted for the use of these drugs in the analyses, it seems unlikely that the observed association was due to fetal exposure to these drugs. However, we cannot completely rule out some residual confounding, as we had no detailed information on the type of antibiotics used (i.e. whether broad-spectrum antibiotics were used), doses and frequency of administration to further adjust the analyses.

The mechanism through which febrile infections in pregnancy may increase the risk of eczema in children is not clear. Infections or fever could act directly or indirectly, exposing the fetus to exogenous toxins or to mediators of inflammation released through or from the placenta (21).

The skin of the fetus is highly permeable to components of the amniotic fluid during early pregnancy, and cytokines from the surrounding micro-environment could be absorbed in immunoreactive forms (2). Exposure to high levels of pro-inflammatory cytokines following maternal infections may have dramatic consequences in the early programming of the developing immune system (2).

Maternal gynecological infections and childhood eczema

In our sample, 6.1% of pregnancies were reported to have been complicated by a gynecological infection, which were associated with a + 82% increased risk of developing eczema in the offspring. In particular, the risk of eczema was nearly threefold greater (+173%) when gynecological infections occurred in the 3rd trimester of pregnancy while they were not associated with eczema when occurring in the 1st or 2nd trimesters.

Some authors have identified the use of broad-spectrum antibiotics as a possible link between gynecological infections and atopic disorders in children (15, 22). In our study, however, gynecological infections were significantly associated with childhood eczema even after adjusting for the use of the antibiotics during pregnancy, suggesting that gynecological infections *per se* might be an independent risk factor for eczema in children. However, as discussed before, we cannot completely rule out some residual confounding, as we had missing information on the specific type of antibiotics used and on the frequency of administration.

It has been reported that microbiota colonizing the cervical and vaginal tract of the mother contribute to the formation of the gut microbiota of the infant (23, 24). According to the so-called microbiota hypothesis, this early colonization of the gut influences the physiological building of immune tolerance and shaping of the immune system (25, 26).

Our findings seem to suggest that the lack of transfer of beneficial microbes such as Lactobacilli or, vice versa, the transmission of harmful vaginal microbiota from a maternal vaginal dysbiosis, may affect the development of a healthy gut microbiota in the infant. This, in turn, may impair the maturation of the immune system, potentially promoting hyper-responsiveness to stressors and the development of atopic disorders (15, 17, 27).

Vaginally delivered infants initially develop bacterial communities resembling maternal vaginal microbiome (i.e., Lactobacillus), as compared to infants born by cesarean section who have bacterial communities similar to those found on their mother's skin surface (i.e., Staphylococcus, *C difficile*) (23, 28). Moreover, differences in the gut microbiome composition were observed between 7-year-old children born by vaginal delivery compared with cesarean section delivered children(29), suggesting that birth events might have effects that persist through childhood.

If the hypothesis of gut colonization by vaginal microbiota as a risk factor for childhood eczema was true, a difference in the effect of gynecological infections between children delivered vaginally and by cesarean section would be observed. In a *post hoc* analysis (Fig S1 in the online data supplement), we found that among the children whose mothers had reported gynecological infections in the 3rd trimester, those born by cesarean section had a lower prevalence of eczema compared with those born by natural delivery through the vagina (45 vs. 31%, respectively), even if the difference was not statistically significant ($p = 0.181$). Further research should identify the specific microbial species involved (if any) and whether treating gynecological infections occurring in the 3rd pregnancy trimester can reduce the risk of atopic disorders in the offspring.

Limits and merits

The main limitation of this study is that birth and pregnancy characteristics were collected retrospectively using a parental self-administered questionnaire. This may raise issues of recall bias, especially in the parents of children who have some health problems. However, the pregnancy events considered (i.e. hypertension and preeclampsia, the occurrence of febrile or gynecological infections for which a mother had to take medicines) have a strong impact on a mother's life and are likely to be precisely recalled. It has also been shown that there is great reliability and validity in recollection of medical complications during pregnancy or delivery when using administered questionnaires (30). Hence, the distortion of our estimates due to the recall bias could be of a relatively minor degree.

Another limit of the study is the lack of detailed information about the type of febrile or gynecological infections suffered. Consequently, this made it impossible to evaluate whether the observed associations with childhood eczema are due to presence or lack of specific pathogens or bacterial microbiota (23, 26, 28). One of the strengths of this survey is that it investigated the whole pediatric population (n = 3907) of the region of Viadana through a questionnaire design that was previously validated in large international studies (12, 13), obtaining a response rate of 98.6%. The collaboration of the school and local health unit personnel was strategic to achieve this outstanding response rate and avoid issues of the selection bias.

Conclusions

These results suggest that fetal exposure to febrile and gynecological infections could increase the risk of developing eczema in childhood. Different trimesters were involved, suggesting that different fetal exposures may interfere with fetal and perinatal programming of skin and immune function through different mechanisms.

The finding of an increased risk of eczema for children born to mothers with gynecological infections raises the hypothesis that exposure to altered vaginal pathogens may interfere with the physiological development of an infant's microbiome and with the maturation of immune tolerance.

Careful medical attention and adequate treatment for mothers who suffer from gynecological infections at the end of the pregnancy may reduce the risk of eczema in the offspring.

Disclosure

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Prevalence of childhood eczema in children born to mothers who did and did not suffer from gynecological infections (GI) during the 3rd trimester of pregnancy, stratified by mode of delivery (natural or cesarean section).

Table S1. Prevalence of childhood eczema (affirmative answer to the question: "has your child ever had eczema?") in children born to mothers who suffered pregnancy complications, stratified by timing of exposure, and odds ratios (OR with 95%CI) for the associations (OR with 95%CI).