

Disclosure of potential conflict of interest: C. C. Miller has received research support from the National Institutes of Health. S. N. Blair has received research support from BodyMedia, the National Institutes of Health, CocaCola, and the National Swimming Pool Foundation and has served as an expert witness on the topic of physical activity programs. The rest of the authors have declared that they have no conflict of interest. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the University of South Carolina or the Centers for Disease Control and Prevention.

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doi:10.1016/j.jaci.2009.10.040

Fetal origin of atopic dermatitis

To the Editor:

Environmental challenges during pregnancy and early life events have long been hypothesized to modulate the susceptibility to chronic diseases in later life, which is commonly referred to as “developmental programming.”¹ The unprecedented rise of allergies occurring in industrialized countries over the past 5 decades² and the recognition that prenatal and postnatal environmental factors³⁻⁵ are involved in the risk to develop allergies suggest that atopic diseases may be central in understanding mechanisms involved in developmental programming.

To date, insights on prenatal maternal biomarkers involved in developmental programming of the fetus are largely elusive. During early pregnancy, hormonal adaptations such as the secretion of progesterone and estradiol are central in establishing adaptation to pregnancy and hence set the stage for a normally progressing pregnancy.⁶ Progesterone is an upstream mediator in the cascade of maternal immune adaptation to pregnancy, and low levels of progesterone can be observed on stress challenge.⁶ Estradiol is pivotal in regulating placental steroidogenic maturation and involved in the development of functional adrenal glands.⁷

We here report an inverse association between levels of maternal progesterone during early pregnancy and the risk for atopic dermatitis in later life of the children. This association was exclusively detectable in girls (Table I), and low levels of maternal progesterone did not affect the risk to develop atopic dermatitis in boys. Interestingly, maternal levels of estradiol during pregnancy were not associated with an altered risk for atopic dermatitis in the children, irrespective of the sex. As expected from published data, parental history of atopic diseases also augmented

the risk for atopic dermatitis in all children (Table I). For additional information, such as patient selection criteria, statistical analyses, see this article’s Methods section in the Online Repository at www.jacionline.org. Additional analyses of potential risk factors considered in this study are provided in this article’s Tables E1 and E2 in the Online Repository at www.jacionline.org.

Multiple logistic regression analyses also confirmed that increasing maternal progesterone levels during early pregnancy significantly reduced the odds to develop atopic dermatitis in girls (adjusted odds ratio, 0.83; 0.73-0.94 CI), whereas no association between maternal progesterone and the development of atopic dermatitis during the first 3 years of life could be seen in boys (adjusted odds ratio, 0.99; 0.93-1.06 CI). See this article’s Table E3 in the Online Repository at www.jacionline.org.

The phenotype of atopic dermatitis between boys and girls did not significantly differ with regard to clinical comorbidity symptoms (Table II), which allows us to exclude a sex-dependent deviation of the disease. Also, significant modulations of maternal progesterone levels by the sex of the fetus could be excluded (17.0 ± 0.8 ng progesterone/mL serum in boy pregnancies vs 17.6 ± 8.3 ng/mL in pregnant women carrying a girl). Similarly, maternal atopy did not significantly influence progesterone levels during pregnancy (16.9 ± 6.6 ng/mL in atopic mothers vs 17.3 ± 8.2 ng/mL in nonatopic mothers).

Our findings suggest that low levels of progesterone may have a predictive value as a marker for an increased risk for atopic dermatitis in girls in early childhood. Because progesterone is well accepted to promote fetal tolerance, it is conceivable that low progesterone levels during early pregnancy challenge the immune tolerance required to sustain an optimal fetal development.

Maternal levels of estradiol did not have any effect on the risk for atopic dermatitis in both sexes. Given the strong immunomodulatory properties of estradiol,⁷ it could be a worthwhile subject of future investigations to test whether maternal levels of estradiol might be involved in the fetal programming toward other diseases.

One central question arising from our observations is the identification of the causes for low maternal progesterone levels. Activation of the hypothalamic-pituitary-adrenal axis by perceived stress and increased levels of stress hormones have been reported to downregulate levels of progesterone. Hence, progesterone could be seen as an endocrine “stress-sentinel.”⁶ Unfortunately, serum progesterone level testing is rarely included in the clinical blood work during early pregnancy, which is somewhat puzzling because progesterone is a recognized adjunct marker for the prediction of early pregnancy outcome.⁶

The inverse association reported here of low levels of progesterone and a high risk for atopic dermatitis in girls in later life is not only of interest as a potential risk indicator for allergies but might also offer a therapeutic opportunity for primary prevention of atopic dermatitis in girls. In a murine experimental model of stress-induced decrease of progesterone during gestation, the supplementation of progesterone with a progesterone derivative called dydrogesterone has been shown to restore mediators of fetomaternal tolerance. Further, the increased allergic airway responsiveness seen in prenatally stressed offspring⁸ can be abrogated by supplementation with a progesterone derivative (unpublished data, Pincus, Bruenahl & Arck, August 2009). This suggests that supplementation of progesterone in women pregnant with a girl may decrease the risk for atopic dermatitis in later life of these girls. If confirmed in independent cohorts, this would evidently be a novel therapeutic intervention aiming at primary prevention of atopic

TABLE I. Univariate analyses of the odds for a child to have atopic dermatitis at the age 0 to 3 years, dependent on child's sex

Parameters	Boys (n = 149)			Girls (n = 124)		
	Crude OR	95% CI	P value	Crude OR	95% CI	P value
Maternal						
Mother's age (y)*	0.99	0.90-1.08	.75	0.96	0.87-1.07	.46
BMI (kg/m ²)†						
< 18.5	3.54	0.47-26.5	.22	NE	NE	NE
18.5-25.0	1	—	—	1	—	—
25.0-30.0	0.30	0.04-2.39	.25	0.59	0.12-2.84	.51
> 30.0	0.20	0.03-1.55	.12	NE	NE	NE
QoL‡	1.00	0.95-1.06	.95	0.99	0.93-1.05	.70
Gestational age (wk)†,‡,§	0.93	0.76-1.15	.52	0.83	0.65-1.05	.11
Smoking during pregnancy						
Yes	NE	NE	NE	0.53	0.11-2.50	.43
No	—	—	—	1	—	—
Endocrine						
Progesterone (ng/mL)†,‡	0.99	0.93-1.05	.65	0.84	0.75-0.95	.003
Estradiol (ng/mL)†,‡	1.00	0.99-1.00	.87	1.00	0.99-1.00	.40
Perinatal						
Duration of pregnancy	1.24	0.93-1.66	.15	1.01	0.78-1.31	.93
Fetal birth weight (g)						
≤ 2800	1.67	0.49-5.79	.41	0.68	0.14-3.27	.63
2801-4200	1	—	—	1	—	—
> 4200	1.99	0.48-8.29	.35	1.59	0.48-8.29	.70
Breast-feeding duration (mo)‡	1.07	0.99-1.15	.08	1.00	0.93-1.81	.94
Parental						
Parental allergy						
2 allergic parents	7.18	2.16-23.8	.012	3.89	0.76-19.8	.10
1 allergic parent	4.07	1.36-12.15	.001	0.89	0.31-2.41	.78
No allergic parent	1	—	—	1	—	—
Parents' educational attainment (y)						
≥ 12	1.92	0.85-4.35	.12	0.58	0.21-1.62	.30
<12	1	—	—	1	—	—
Environmental						
Postnatal parental smoking¶						
Regular	0.37	0.12-1.14	.08	0.91	0.30-2.78	.87
Irregular	NE	NE	NE	1.41	0.26-7.51	.69
Never	1	—	—	1	—	—
Older siblings#	0.74	0.38-1.42	.36	1.12	0.55-2.30	.75
Day care attendance‡ (mo)	1.03	0.98-1.09	.24	0.97	0.92-1.04	.40
Cat ownership**						
Yes	0.46	0.13-1.65	.23	0.39	0.08-1.79	.23
No	1	—	—	1	—	—

BMI, Body mass index; NE, not estimable; OR, odds ratio; QoL, quality of life.

*At birth of child.

†At recruitment during first trimester.

‡Per unit increase.

§When progesterone was assessed.

||Minimum 28 weeks, maximum 43 weeks.

¶Detail on the definition of this parameter are described under 'Potential confounders' in the online repository.

#Per additional sibling.

**Cat in household during the first 3 years. Dogs were not evaluated because the number was insufficient.

dermatitis in girls. The potential risks of progesterone intervention at the early stages of human pregnancy has recently been thoroughly evaluated in a Cochrane review, and the meta-analysis revealed that prenatal administration of progesterone appears to lower the rate of preterm birth and low birth weight and bears no risk for the fetus in singleton pregnancies.⁹

Our current report suggests that in future birth cohort studies—preferentially with a recruitment time point during the first trimester or even before conception—serum progesterone level should be monitored and validated as a reliable and sensitive risk indicator for the subsequent development of atopic dermatitis in girls. Also, analyses of additional markers during gestation, such

TABLE II. Incidence, phenotype, and clinical feature–based severity of atopic dermatitis during the first 3 years of life, stratified for boys and girls

Clinical feature	Boys (n = 34)	Girls (n = 26)	P value
Current atopic dermatitis* (%)	65	54	.395
Atopic dermatitis severity score (median; mean $\pm$ SD)	2.4; 6.8 $\pm$ 9.6	2.1; 9.3 $\pm$ 14.3	.864
Wheezing (%)	41	42	.930
Allergic rhinitis (%)	18	15	.816
Food allergy (%)	29	17	.301
Urticaria (%)	27	23	.764

*Defined as atopic dermatitis that lasted over a period of the last 12 months.

as maternal serum levels of cortisol, progesterone metabolites, and testosterone, along with markers for epigenetic modulations in mother and child merit consideration. Further, genetic analyses for polymorphisms identifying high-risk children, continuous IgE levels in parents and children, and documentation of nutritional habits should be thoroughly evaluated in such birth cohorts. This will improve our understanding of mechanisms involved in developmental programming of allergies. Further, basic and clinical research follow-up studies should focus on progesterone-mediated signaling and progesterone supplementation in the context of neonatal immune maturation, aiming at developing primary prevention strategies of atopic dermatitis in girls.

We are indebted to the support of the 99 clinicians in private practice in Berlin and their staff. Without their enthusiasm, it would have been impossible to perform the current study.

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Supported by research grants from the Charité (KKS), the Alexander-von-Humboldt Foundation, the German Research Foundation, and AllerGen NCE Canada. M.P. is supported by the Rahel Hirsch Program, awarded by the Charité.

Disclosure of potential conflict of interest: M. Pincus has received research support from Deutsche Forschungsgemeinschaft and Alexander von Humboldt Stiftung. P. Arck has received research support from AllerGen NCE, the Banting Foundation, the German Research Foundation, the Canadian Institute for Health Research, the Alexander von Humboldt Foundation, and Charité University Medicine Berlin. A. J. Douglas has received research support from the Medical Research Council UK, the Wellcome Trust, and the Society for Endocrinology UK. The rest of the authors have declared that they have no conflict of interest.

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doi:10.1016/j.jaci.2009.10.057

METHODS

Study design and setting

The birth cohort study was carried out by recruiting pregnant women during the first trimester in obstetrical practices in Berlin, Germany, from February 2002 until August 2003.

Participants

Recruitment of pregnant women was carried out by 99 obstetricians in private practice in Berlin, Germany. The obstetricians were asked to recruit women who had scheduled an appointment to obtain confirmation of pregnancy. If pregnancy could be confirmed by a positive urine test or via ultrasound at the recruitment visit, women were eligible to participate in the current study. Women who were already beyond the 12th week of gestation, or enrolled in an *in vitro* fertilization program were excluded from the study. High-risk pregnancies because of a history of recurrent spontaneous abortion, amnion infection, or women testing positive for hepatitis B/C or HIV were exclusionary. Because of the geographic distribution of the recruiting obstetricians over the various districts of Berlin, we were able to recruit women from a range of social backgrounds and hence consider our study population to mirror a general urban population of western countries. Medical, obstetric, and gynecologic history and demographic details were thoroughly documented at recruitment and during the follow-ups. A variety of parental diseases were documented, including the detailed evaluation of parental allergic manifestations. To avoid a skew toward a biased recruitment of parental subjects with allergy, which would subsequently bias the general allergy prevalence in children, we also thoroughly evaluated additional clinical aspects, such as psychiatric disorders. Standardized questionnaires were used to evaluate maternal quality of life (QoL-PCS) and social support. Further, blood was taken at recruitment by venous puncture from all women and delivered to our laboratory within 1 to 3 hours by courier. Serum was harvested from all blood samples after centrifugation (2000 rpm/20 minutes) and stored at -80°C until further use.

The study was originally designed to identify early markers for subsequent pregnancy complications. Initially, 1098 pregnant women had been recruited and were followed up until pregnancy completion.^{E1,E2} Shortly after delivery, the families had been approached by our study center to enroll them for the continuation of the study, evaluating the children's health. In 473 cases, families had agreed to be continuously contacted and hence were contacted on an annual basis. A total of 353 families participated until the children's age of 3 years (Table E1). Our primary hypothesis of this study continuation was to benefit from the readily available data documented during early pregnancy and link them to the prospectively obtained insights on children's health. The research protocol of the initial study and the continuation were approved by the ethics committee of the Charité University Medicine Berlin and its Center for Coordination of Clinical Studies. All participants gave written informed consent.

Outcome variable

The cumulative incidence of atopic dermatitis in the children from birth to the age of 3 years was defined as the outcome. All participating women were contacted by mail at the age of 3 years. The questionnaires sent to the participants to evaluate the incidence of early childhood diseases included the German translation of the question, "Has a doctor ever diagnosed atopic dermatitis in your child?" If the answer to this question was yes, these study participants were assigned to the group of patients with atopic dermatitis. This assignment was supported by information given by the parents on whether and how severely the child has/had atopic dermatitis. The severity of atopic dermatitis was further evaluated by using the Self-administered Eczema Area and Severity Index Questionnaire (SA-EASI), a 1-page instrument in which caregivers of children with atopic dermatitis can provide details on the disease severity.^{E3}

Exposure of interest

Maternal serum progesterone and estradiol levels during the first trimester were analyzed by using commercially available ELISA kits (DRG Instruments GmbH, Marburg, Germany). Serum samples were thawed and—if required by the kit's protocol—steroids were extracted and assayed according to the manual provided by the manufacturer.

Potential confounders

Maternal characteristics such as age, body mass index, quality of life, the gestational age at time of recruitment, and smoking habits during and after pregnancy were considered as potential confounders and had been documented at recruitment and during the follow-ups. Further, additional parameters including the gestational age at time of delivery, cesarean section, fetal birth weight, and nutrition (breast-feeding or formula-feeding, duration of breast-feeding, mastitis) were taken into account in the statistical analysis. Also, parental characteristics such as allergies, educational background (which was defined as education more than 12 years or less than 12 years of the mother), and postnatal environmental challenges including the presence of older siblings, pet contact, and day care attendance were evaluated, given that these factors may influence the risk of allergies in children. Postnatal tobacco smoke exposure was defined as "regular" when the mother reported smoking at 2 or all 3 follow-up assessments, as "irregular" when she reported smoking at only 1 of the 3 assessments, and "never" if she reported not smoking at the 3 postnatal follow-up assessments. Similarly, we defined tobacco smoke exposure during pregnancy according to the mother's smoking habits.

Statistical methods

For descriptive analyses, we calculated medians, means, and SDs for progesterone, estradiol, and other continuous variables. Differences between study participants who were included in the analysis and those who were lost to follow-up were tested by the χ^2 test (for categorical variables) and the Mann-Whitney *U* test (for continuous variables). We calculated crude odds ratios with 95% CIs as a measure of uncertainty to estimate the association between progesterone and atopic dermatitis for all children combined (Table E2). In multiple regression analyses, we calculated odds ratios and 95% CIs adjusting for potential confounders based on the literature (Table E3). The adjusted model included gestational age when progesterone was assessed (in weeks), parental allergy status (2 and 1 vs parents without allergy), parental educational attainment (≥ 12 vs < 12 years of schooling), maternal smoking during pregnancy (yes vs no), postnatal maternal smoking (regular and irregular smoking during study follow-up vs never smoked), number of older siblings, and cat contact (yes vs no). All calculations were performed using the statistical software package SPSS 14.0 (SPSS Inc, Chicago, Ill).

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TABLE E1. Comparison of demographic, anamnestic and psychosocial parameters at time of recruitment between continuously participating families compared to discontinued participation

Parameter*	Continuous participation	Discontinued participation	P value
Maternal age (y)	29.7 ± 0.3	28.3 ± 0.5	.008
(available data)	353	120	
BMI (kg/m ²)	23.3 ± 0.23	23.4 ± 0.4	.780
(available data)	344	115	
Gestational age at recruitment (wk)	8.4 ± 0.1	8.05 ± 0.2	.138
(available data)	353	120	
Progesterone (ng/mL)	17.3 ± 0.4	17.6 ± 0.9	.960
(available data)	337	113	
QOL-PCS (score)	49.7 ± 0.4	49.2 ± 0.7	.632
(available data)	353	120	
Social support (score from 1 to 5)	4.5 ± 0.03	4.6 ± 0.04	.383
(available data)	327	105	
Estradiol (pg/mL)	638.5 ± 30.2	650.6 ± 56.4	.908
(available data)	303	107	
Week of delivery	39.6 ± 0.01	39.4 ± 0.2	.260
(available data)	350	112	
Fetal birth weight (g)	3427.8 ± 28.6	3388.9 ± 48.5	.532
(available data)	353	115	
Twin—fetal birth weight (g)	1855.0 ± 515.0	2250 ± 224.1	.537
(available data)	2	4	
Education (≥12 years of schooling, %)	37.3	26.1	.025
(available data)	351	119	
Study children with older siblings (%)	39.7	41.0	.830
(available data)	320	79	
Mothers who are employed (%)	87.5	75.4	.002
(available data)	307	89	

*If not stated differently, parameter are described as mean ± SEMs; available data indicate number.

TABLE E2. Univariate analyses of the odds for a child to have atopic dermatitis at the age 0 to 3 years

Parameters	Crude OR	95% CI	P value
Maternal			
Age (y)*	0.98	0.91-1.04	.48
BMI (kg/m ²)†			
<18.5	1.53	0.29-8.14	.62
18.5-25.0	1	—	—
25.0-30.0	0.44	0.13-1.52	.20
>30.0	0.17	0.02-1.26	.08
QoL-PCS‡	1.00	0.96-1.04	.81
Gestational age†,‡,§	0.89	0.76-1.04	.126
Social support	1.26	0.68-2.33	.467
Smoking during pregnancy			
Yes	0.22	0.05-0.93	.04
No	1	—	—
Endocrine			
Progesterone (ng/mL)†,‡	0.94	0.89-0.99	.02
Estradiol (ng/mL)†,‡	1.00	0.99-1.00	.13
Perinatal			
Duration of pregnancy†,	1.12	0.92-1.36	.25
Fetal birth weight (g)			
≤2800 g	1.13	0.43-2.93	.81
2801-4200	1	—	—
>4200	1.88	0.56-6.30	.31
Breast feeding duration‡ (mo)	1.03	0.98-1.09	.19
Parental			
Parental allergy			
2 allergic parents	4.57	1.92-10.8	.001
1 allergic parent	1.84	0.91-3.74	.090
No allergic parent	1	—	—
Parents' educational attainment (y)			
≥12	1.18	0.63-2.19	.61
<12	1	—	—
Environmental			
Postnatal parental smoking¶			
Regular	0.56	0.26-1.22	.14
Irregular	0.33	0.08-1.47	.15
Never	1	—	—
Older siblings#	0.89	0.55-1.44	.64
Day care attendance‡ (mo)	1.01	0.97-1.05	.80
Cat contact**			
Yes	0.43	0.16-1.14	.09
No	1	—	—

BMI, Body mass index; OR, odds ratio.

*At birth of child.

†At recruitment during first trimester.

‡Per unit increase.

§When progesterone was assessed.

||Minimum 28 weeks, maximum 43 weeks.

¶Details on definition are provided in Methods.

#Per additional sibling.

**Cat in household during the first 3 years. Dogs were not evaluated because the number was insufficient.

TABLE E3. Odds for a child to develop atopic dermatitis at an age 0 to 3 years, stratified for boys and girls, based on multivariable logistic regression analysis*

Parameters	Boys (n = 149)			Girls (n = 124)		
	Adjusted OR*	95% CI	P value	Adjusted OR*	95% CI	P value
Endocrine						
Progesterone (ng/mL) ^{†,‡}	0.99	0.93-1.06	.78	0.83	0.73-0.94	.004
Gestational age (wk) [§]	0.90	0.79-1.03	.94	0.82	0.62-1.09	.17
Parental						
Parental allergy						
2 allergic parents	5.22	1.43-19.1	.01	4.30	0.56-32.9	.16
1 allergic parent	3.03	0.97-9.44	.05	0.63	0.20-2.03	.44
No allergic parent	1	—	—	1	—	—
Parents' educational attainment (y)						
≥12	1.07	0.44-2.64	.88	0.56	0.18-1.79	.33
≤12	1	—	—	1	—	—
Environmental						
Maternal smoking during pregnancy						
Yes	NE	NE	NE	0.44	0.07-2.98	.40
No	NE	NE	NE	1	—	—
Postnatal parental smoking						
Regular	1.16	0.32-4.26	.82	1.11	0.30-4.18	.88
Irregular	NE	NE	NE	2.45	0.33-17.9	.38
Never	1	—	—	1	—	—
Older vs no older siblings¶	0.85	0.40-1.80	.67	0.85	0.40-1.80	.67
Cat ownership#						
Yes	0.85	0.20-3.57	.82	0.31	0.06-1.71	.18
No	1	—	—	1	—	—

NE, Not estimable; OR, odds ratio.

Statistically significant results are highlighted in boldface.

*Adjusted for all variables listed here.

†At recruitment during first trimester.

‡Per unit increase.

§When progesterone was assessed.

||Details on definition are provided in Methods.

¶Per additional sibling.

#Cat in household during the first 3 years. Dogs were not evaluated because the number was insufficient.