

Maternal sex hormones in early pregnancy and asthma among offspring: A case-control study

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Background: Sex hormones may be associated with the risk of onset of asthma.

Objective: To study the association between maternal sex hormone concentrations during early pregnancy and the risk of asthma among offspring.

Methods: A case-control study of 129 asthmatic children and 125 control children 5 to 6 years of age. Maternal sera in early pregnancy were obtained from the Finnish Maternal Cohort serum bank.

Results: The means of serum progesterone and estradiol in mothers of asthmatic and control children were 81.0 and 82.8 nmol/L ($P = .60$), 7.87 nmol/L and 7.65 nmol/L ($P = .99$), and 149.5 pmol/L and 148.0 pmol/L ($P = .95$), respectively. There were also no differences in the mean concentrations of maternal sex hormones according to the presence of allergic rhinitis or atopic eczema among the children.

Conclusions: The current results do not support an association between maternal sex hormone concentrations during early pregnancy and onset of allergic disease in early childhood. (*J Allergy Clin Immunol* 2003;112:1101-4.)

Key words: Asthma, atopy, allergic disorders, childhood, sex hormones, pregnancy

The key events leading to T_H2-polarized immunity, allergy, and asthma are initiated in utero and during the first year of life.^{1,2} This process is enhanced through the mother's immune system, which, during pregnancy, is deviated toward T_H2 immunity to protect the fetus from the toxic T_H1 cytokines.³

This T_H2 deviation during pregnancy is strongly affected by the levels of sex hormones. Progesterone promotes development of T_H2-type immunity and downregulates T_H1 cells and production of proinflammatory cytokines.⁴ Also, estradiol has several partly conflicting immunogenic effects.^{4,5} It has also been shown that risk of atopy in offspring was linked to low age at menarche of the mother,⁶ a marker of the mother's endogenous estrogen status. The same association has then been observed between the mother's menstrual age and risk of rhinitis.⁷

In adults, both changes in the levels of progesterone and estrogen and use of hormone preparations have been shown to affect both symptoms of asthma and lung function, possibly through an effect on the smooth muscle.^{8,9} However, hormone exposure also might have more long-term effects, as was shown in a prospective study of menopausal women, among whom the risk of asthma was positively associated with estrogen replacement therapy.¹⁰

These findings raise the possibility that levels of progesterone and estrogen during pregnancy may influence the risk of asthma and allergic diseases among the offspring.^{5,11-13} We therefore conducted a case-control study to evaluate the relation of maternal sex hormone concentrations at early pregnancy and the risk of asthma among offspring at the age of 5 to 6 years.

METHODS

Our study used the Finnish Maternity Cohort (FMC) serum bank at the National Public Health Institute. This bank contains serum samples from almost all (99%) pregnant women in Finland since 1983. The samples were drawn at the maternity clinics from women during early pregnancy (first trimester) to screen for congenital infections. At the end of 1993, the bank contained 710,000 serum samples from 390,000 women.¹⁴ In addition, the FMC serum bank contains cord blood samples from 49,680 children born in Finland during September 1, 1992, to August 31, 1993 (70% of all newborn infants). The cord blood samples were drawn at maternity hospitals for screening of hypothyreosis. The serum samples and cord blood samples were stored frozen at -25°C until the current study.

This population cohort born from September 1992 through August 1993 was linked with the register for reimbursement for asthma medication at the Social Security Institution of Finland. In Finland, patients can apply for higher compensation for medication for several chronic diseases from the Social Security Institution, but they need to present a doctor's certificate. For asthma, the certificate generally needs to be written by a specialist, and the disease needs to fulfil strict criteria given by the institution. All such cases of asthma are registered.

Among the children identified to have reimbursement for asthma medication, 800 asthmatic children were randomly selected (Fig 1). In addition, 800 children from the same birth cohort without asthma were randomly selected with frequency matching for age (4 categories, every 3 months) and sex with the asthmatic cases. A questionnaire on children's health history, biological and social environment, parental demographics, and maternal information on pregnancy and delivery was sent to parents of 1600 selected children together with a consent form; 1287 (80.4%) questionnaires were returned, and 1231 of the mothers gave permission to use their stored serum samples and other information in the study. Detailed information on delivery was then obtained through registry linkage with the Finnish birth registry at the Research and Development Centre for Welfare and Health (STAKES). Only singletons ($n = 1182$) with consent were included in the current

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FIG 1. Selection of the study population.

study. The amount of available maternal serum was then checked for 450 randomly selected cases and 450 control children; among these, 1182 singletons and 254 maternal samples with a volume of ≥ 1.5 mL were selected for maternal sex hormone determinations, consisting of 129 cases and 125 control subjects.

There was good agreement between the questionnaire and registry information on asthma. Only one control child had a positive answer to the question "Has your child ever had asthma?" and 4 cases a negative answer. Therefore, questions on asthma were not used in the current analyses. Allergic rhinitis was defined as a positive response to the question: "Has your child ever had hay fever or other allergic rhinitis?" Atopic eczema was defined as a positive response to the question: "Has your child ever had atopic eczema (flexural rash)?"

Concentrations of serum progesterone (nmol/L), total estradiol (nmol/L), and non-protein-bound estradiol (free estradiol) (pmol/L) were measured at the Medix Lab Oy in Turku, Finland. The proportion of free estradiol was estimated on the basis of the measured concentration of sex hormone-binding globulin.

Differences in means of sex hormone concentrations were examined between asthmatic children and control children by means of the nonparametric Kruskal-Wallis test. Odds ratios of asthma, allergic rhinitis, and atopic eczema among children 5 to 6 years of age by tertiles of maternal sex hormone concentrations at early pregnancy were calculated by means of unconditional logistic regression. All analyses were adjusted for the variables used in frequency matching (age and sex of the child) and multivariate analyses for gestational week in which samples were collected, maternal age, maternal history of asthma, allergic rhinitis, or atopic eczema, smoking during pregnancy, and gestational age at birth (above or below 37 weeks). Further adjustment for the mother's marital status, birth weight, or farming did not change the results. Analyses on allergic rhinitis and atopic eczema were also adjusted for asthma status. As sensitivity analyses, the analyses were conducted including only those 202 samples that were collected at the 11th gestational week or earlier, but the results were essentially unchanged.

RESULTS

The mean progesterone and the total estradiol concentrations among 254 serum samples were 81.9 nmol/L (SD, 32.4) and 7.76 nmol/L (SD, 6.95), respectively. Maximum concentration of progesterone was 240.0 nmol/L, and the total estradiol was 60.0 nmol/L. The mean of free estradiol was 149 pmol/L (SD, 122). The hormone concentrations were highly correlated. Spearman rank correlation r was 0.59 for progesterone and total estradiol, 0.58 for progesterone and free estradiol, and 0.996 for total estradiol and free estradiol. Because of the high correlation, free estradiol showed results very similar to total estradiol in all analyses, and only results for total estradiol are shown.

Progesterone and total estradiol concentrations increased markedly if the samples were collected after the 11th gestational week of pregnancy (Table I). Mean hormone concentrations were lower among older mothers (ages ≥ 35 years). Mothers who delivered a female baby tended to have slightly lower mean progesterone concentrations. Conversely, single and smoking mothers tended to have higher estradiol concentrations.

There were no differences in mean maternal sex hormone concentrations in early pregnancy between asthmatic subjects and control subjects; the means of progesterone were 81.0 and 82.8 nmol/L ($P = .60$); of estradiol, 7.87 and 7.65 nmol/L ($P = .99$); and of free estradiol, 149.5 and 148.0 pmol/L ($P = .95$), respectively. There were also no differences in the mean concentrations of maternal sex hormone levels according to the presence of allergic rhinitis or atopic eczema in the child at the age of 5 to 6 years. The prevalence of allergic rhinitis was 59% among cases and 7% among control subjects, and of atopic eczema, 62% and 33%.

Table II presents odds ratios for asthma, allergic rhinitis, and atopic eczema among children by tertiles of maternal sex hormone concentrations, together with ratios

TABLE I. Means of maternal progesterone and estradiol levels at early pregnancy by various covariates

	n	Progesterone (nmol/L)	Estradiol (nmol/L)
Gestational week samples collected			
≤7	20	84.90	6.97
8-9	86	78.24	6.53
10-11	96	76.51	7.26
12-13	23	97.91	10.69
≥14	24	102.21	12.49
P value		.002	<.001
Maternal age			
≤24	59	78.27	9.37
25-29	91	83.36	7.42
30-34	73	88.18	7.82
≥35	31	69.77	5.56
P value		.032	.037
Maternal marriage			
Married	183	82.98	7.44
Single or others	71	79.13	8.58
P value		.611	.063
Maternal smoking during pregnancy			
No	212	82.18	7.41
Smoked or others	42	80.50	9.52
P value		.817	.024
Delivery styles			
Caesarean section	39	74.26	6.56
Vaginal	215	83.29	7.98
P value		.264	.252
Sex of child			
Boys	159	84.76	7.64
Girls	95	77.13	7.96
P value		.071	.969
Birth weight (g)			
≤3000	31	76.61	7.07
3001-3500	63	81.22	8.18
3501-4000	109	83.83	7.42
4001-4500	41	73.98	6.65
≥4501	10	114.20	15.50
P value		.183	.482
Gestational week at birth			
≤37	24	96.29	10.60
38-39	87	79.98	8.21
40-41	127	80.98	7.15
≥42	16	78.13	5.96
P value		.511	.102

Asthma, rhinitis, other
respiratory diseases

of progesterone/estradiol. No significant associations were found except for the increased risk of asthma in the second but not in the third tertile of the ratio of progesterone/estradiol and the reduced risk of atopic eczema in the second tertile of progesterone. Given the lack of dose-response, these associations may be due to chance.

DISCUSSION

In recent years, increasing efforts have been made in evaluating the association between sex hormones and allergic disorders.^{8-9,12} There is some evidence suggesting that hormonal status, timing of ovulation, and use of hormones is linked with severity of asthma and atopy and even with incidence, as observed in the Nurse's Health study.¹⁰ However, the results are quite inconsistent.⁸ Sex

hormones have also several immunogenic effects⁴ and may promote the development of T_H2-type immunity in the fetus.^{5,11-13} However, the current results do not suggest any substantial relation between maternal sex hormone concentrations in early pregnancy and the risk of allergic disorders among children at the age of 5 to 6 years.

To our knowledge, this is the first study evaluating the association between measured sex hormone concentrations during pregnancy and the risk of development of asthma or other allergic diseases among children. The definition of asthma was based on strict criteria, that is, reimbursement for medication for asthma. However, we studied children 5 to 6 years of age, and asthma at this age may not always indicate persistent asthma. Also, allergic rhinitis might not have developed in many children at this age. Therefore, the current study cannot rule

TABLE II. Odds ratios* of allergic diseases among 254† children 5 to 6 years of age by tertiles of maternal progesterone and estradiol levels at early pregnancy

	Asthma		Allergic rhinitis		Atopic eczema	
	Crude OR (95% CI)	Multivariate OR (95% CI)	Crude OR (95% CI)	Multivariate OR* (95% CI)	Crude OR (95% CI)	Multivariate OR* (95% CI)
Progesterone (nmol/L)						
1 (≤64)	1.00	1.00	1.00	1.00	1.00	1.00
2 (65-91)	1.38 (0.75, 2.56)	1.22 (0.64, 2.34)	0.64 (0.29, 1.42)	0.54 (0.23, 1.25)	0.52 (0.27, 1.00)	0.49 (0.25, 0.97)
3 (≥92)	0.87 (0.47, 1.62)	0.92 (0.47, 1.79)	0.45 (0.19, 1.05)	0.54 (0.22, 1.31)	0.70 (3.64, 1.35)	0.74 (0.37, 1.47)
Estradiol (nmol/L)						
1 (≤3.96)	1.00	1.00	1.00	1.00	1.00	1.00
2 (3.97-7.78)	0.92 (0.50, 1.70)	0.99 (0.51, 1.91)	0.76 (0.34, 1.70)	0.83 (0.36, 1.90)	1.14 (0.60, 2.17)	1.10 (0.56, 2.17)
3 (≥7.79)	0.91 (0.49, 1.67)	0.86 (0.43, 1.71)	0.71 (0.32, 1.60)	0.71 (0.30, 1.70)	0.77 (0.40, 1.46)	0.75 (0.37, 1.53)
Ratio of progesterone/estradiol						
1 (≤10.28)	1.00	1.00	1.00	1.00	1.00	1.00
2 (10.29-17.27)	1.89 (1.01, 3.51)	1.93 (0.99, 3.78)	0.98 (0.43, 2.23)	0.99 (0.42, 2.35)	1.19 (0.62, 2.28)	1.15 (0.58, 2.28)
3 (≥17.28)	0.93 (0.50, 1.72)	1.06 (0.52, 2.16)	1.48 (0.63, 3.45)	1.67 (0.66, 4.27)	1.29 (0.68, 2.47)	1.22 (0.59, 2.51)

*All odds ratios adjusted for variables used in frequency matching (age and sex) and analyses of allergic rhinitis and atopic eczema also for asthma status. Multivariate odds ratios adjusted also for gestational week in which samples were collected, maternal age and smoking, gestational age at birth, and maternal history of allergic disease.

†Because of missing data, the number of observations in the different models range between 244 and 254.

out the possibility that maternal sex hormone concentrations would have an effect on the child's tendency to development of atopic diseases later in life. For example, it might be possible that the association appears only after the child has undergone puberty or enters adulthood.¹⁰ Alternatively, hormone levels in late pregnancy may be more important than levels in early pregnancy, as studied in the current study.

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