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Original article

Preconceptional exposure to oral contraceptive pills and the risk of wheeze, asthma and rhinitis in children

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OCP	oral contraceptive pills
ISAAC	the International Study of Asthma and Allergies in Childhood
BMI	Body Mass Index
DOHaD	Developmental Origins of Health and Disease

ABSTRACT

Background: The prevalence of maternal oral contraceptive pills (OCP) use and that of childhood asthma are high in western countries. The aim of this study is to examine the association of OCP use with childhood wheeze and allergic diseases in Japan.

Methods: Relevant data were extracted from a hospital based birth cohort study named as Tokyo-Children's Health, Illness and Development Study (T-CHILD) of which questionnaire conducted during pregnancy included maternal history and duration of OCP use. To identify wheeze and allergic diseases in the children, the questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) was used. Logistic regression models were applied to estimate those association and adjustments were made for maternal history of allergy, maternal education level, maternal age at pregnancy, maternal BMI, maternal smoking during pregnancy, mode of delivery, gestational age at delivery, daycare attendance, number of previous live births, and gender of child.

Results: OCP use was associated with ever wheeze (adjusted odds ratio [aOR], 1.62; 95% confidence interval [CI], 1.10–2.40), current wheeze (aOR, 1.59; 95% CI, 1.01–2.50), ever asthma (aOR, 1.65; 95% CI, 1.02–2.65), and ever rhinitis (aOR, 1.90; 95% CI, 1.30–2.80). Compared with no prior OCP use, using OCP for more than three months statistically increased the odds of ever wheeze ($P = 0.012$), current wheeze ($P = 0.035$), and ever rhinitis ($P = 0.002$).

Conclusions: Our findings suggest that maternal OCP use has a role in the development of wheeze, asthma and rhinitis in children. Extended use of OCP is likely to increase the risk of wheeze and rhinitis.

Introduction

First wave of allergic epidemic occurred in westernized countries including Japan drew attention mainly on asthma and its prevalence has reached high plateau in recent decades,[1] followed by second wave from developing countries. Although Japan has been a top runner of this undesirable race in the Asia-Pacific region, now prevalence of allergic diseases such as asthma, atopic eczema, and rhinoconjunctivitis among young schoolchildren have become high in many countries in this region.[2,3] Environmental changes elicited by rapid industrialization and affluent life might have interacted genetic function resulting in the epidemic of asthma and allergic diseases.[4]

The emerging concept of Developmental Origins of Health and Disease (DOHaD) hypothesis suggests that various environmental exposures during preconceptional and postconceptional period for embryo and fetus may contribute to development of non-communicable diseases for children.[5,6] The cause and development of allergy are complicated and need further investigation.

In western affluent countries, oral contraceptive pills (OCP) use has become common and an association of OCP use with childhood wheeze and asthma was reported in several studies from western countries, although conclusions were mixed.[7–9] The aim of our study was to elucidate the relationship between OCP use and

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childhood asthma and allergic disease in Japan located outside region of western countries.

We examined whether a history of maternal OCP use and the duration of the usage before pregnancy were associated with wheeze and allergic features in five-year-old children.

Methods

Study design was a hospital based prospective birth cohort study, which was named as Tokyo-Children's Health, Illness and Development study (T-CHILD study).[10,11] We recruited 1701 pregnant women at the first antenatal visit at the National Center for Child Health and Development (NCCHD) in Tokyo Japan between 2003 and 2005. Among neonates born from these women, a total of 1550 newborn babies and their mothers were registered in this cohort from March 2004 to August 2006. Baseline data were collected from questionnaires answered by mothers during pregnancy and their medical charts. Outcome data of children at 5 years old were obtained from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire which was translated into Japanese and validated through the process of back translation under cooperation of the sterling committee members. The definitions of outcomes and exposures are described in Table 1. Potential confounders were maternal history of allergy (asthma, atopic dermatitis, or allergic rhinitis), maternal education level, maternal age at delivery, maternal body mass index (BMI) at recruitment, maternal smoking during pregnancy, caesarean section, gestational age at delivery, number of previous live births, daycare attendance at age of one and gender.

Table 1
Definitions of outcomes and exposures.

Outcomes of children at five years old	
Wheeze ever	a positive answer to the question at five years old of the children: "Has your child ever had wheezing or whistling in the chest at any time in the past?"
Wheeze current	a positive answer to the question at five years old of the children: "Has your child ever had wheezing or whistling in the past 12 months?"
Asthma ever	a positive answer to the question at five years old of the children: "Have you ever had asthma?"
Asthma current	a positive answer to the question at five years old of the children: "Has your child ever been diagnosed by a doctor as having asthma in the past 12 months?"
Rhinitis ever	a positive answer to the question at five years old of the children: "Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?"
Rhinitis current	a positive answer to the question at five years old of the children: "In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?"
Eczema ever	a positive answer to the question at five years old of the children: "Have your child ever had eczema?"
Eczema current	a positive answer to the question at five years old of the children: "Has your child had this itchy rash at any time in the past 12 months?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?"
Exposures of COP	
Past history of OCP use	a positive answer to the question of the base line data, "Have you ever used the pill?".
Duration of OCP use	a positive answer to the question of the base line data, "How long have you ever used the pill totally?" and it was classified into three groups, (not use, OCP 1–6 months use and OCP >6 months use).

Data from surveys conducted at pregnancy and children at age of five were used for analysis of the current study. Data of Twins and those with missing values were not included for analysis.

For statistical analysis, the differences in patient characteristics between OCPs and non-OCPs groups were tested using the chi-square test and t-test for category variables and continuous variables, respectively. Univariate and multivariate logistic regression analyses were used to analyze the association between maternal OCP use and allergic diseases in children. The potential confounders were included in multivariate models to obtain the adjusted odds ratios (aORs). We also performed a trend test for duration of OCP use with the logistic model by treating duration of OCP, the ordered variable, as continuous variables. All associations based on models were presented with odds ratios with 95% confidence intervals (CI). Statistical analyses were conducted using SPSS Version 22.0 (IBM Corp. Armonk, NY, USA), with a *P*-value of <0.05 defined as being statistically significant.

Results

We obtained the data of 980 children without missing variables. The comparison of subjects analyzed in our study with those who were excluded revealed that a difference only in parity (see Table 2). Table 3-1 and Table 3-2 showed the characteristics of the participants according to OCP users and duration of OCP users. There were statistically significant differences for maternal age at pregnancy, number of previous live births, type of delivery and child's gender and daycare attendance in background characteristics between OCP use group and non-OCP use group. Of the children, 28.2% had a history of ever wheeze and 15.9% had current wheeze, and 14.6% had ever asthma and 10.2% had current asthma, at five years old. Among the mothers, 13.8% had a past history of OCP use and 6.2% used OCP for more than three months in total.

Table 4 showed the association of maternal OCP use before pregnancy with childhood wheeze and allergic outcomes. In the adjusted analysis, maternal OCP was associated with an increased risk of ever wheeze (aOR, 1.62; 95% CI, 1.10–2.40), current wheeze (aOR, 1.59; 95% CI, 1.01–2.50), ever asthma (aOR, 1.65; 95% CI, 1.02–2.65) and ever rhinitis (aOR, 1.90; 95% CI, 1.30–2.80).

Table 5 showed the association of OCP use duration before pregnancy with childhood wheeze and allergic outcomes. In adjusted analysis, a usage of OCP of more than three months statistically was associated with an increased risk of ever wheeze

Table 2
Comparison between the characteristics of participants included in the analysis and those of lost follow up.

	Data used for analysis			Data not used for analysis			*P*
	n	N	%	n	N	%	
Maternal characteristics							
OCP use (yes)	135	980	13.8	65	475	13.7	0.962
Maternal history of allergy (yes)	547	980	55.8	227	417	54.4	0.653
Level of education							
Middle school or high school	98	980	10	42	411	10.2	0.901
Body mass index at pregnancy (≧25)	46	980	4.7	27	480	5.6	0.443
Smoking during pregnancy	22	980	2.2	16	476	3.4	0.210
Maternal age at pregnancy (≧35)	407	980	41.5	188	479	39.2	0.405
Number of previous live births (≧1)	424	980	43.3	263	479	54.9	<0.001
Caesarean section	216	980	22	104	475	21.9	0.950
Gender (Male)	500	980	51	261	480	54.4	0.228
Daycare (yes)	206	980	21	62	319	19.4	0.544
Weeks of gestation, median (IQR)	39 (38, 40)			39 (38, 40)			0.120[†]

[†] Mann–Whitney test. IQR, Interquartile range25th, 75th.