

Original article

Maternal oral contraceptive use and atopic diseases in the offspring

Background: This study examined the association of maternal oral contraceptive (OC) use – before and after birth – and atopic manifestations in the offspring.

Methods: A total of 2754 East German children aged 5–14 years participated in a cross-sectional survey in 1998–99. The standardized parental questionnaire in 1998–99 included data on atopic diseases, socio-economic factors, parental atopy and maternal OC use. Specific immunoglobulin E against common inhalant allergens was measured by radioallergosorbent test (RAST).

Results: Maternal OC use before birth was associated with a higher risk of atopic diseases in the offspring compared with children of mothers who had never taken OC [asthma: odds ratio (OR) 1.6; 95% confidence interval (CI): 0.9–3.0; allergic rhinitis: OR 1.5; CI: 0.96–2.2; atopic eczema: OR 2.6; CI: 1.6–4.3; atopic sensitization: OR 1.5; CI: 0.97–2.2]. However, the effect estimates for maternal OC use after birth compared with the never users showed quite similar effects for these atopic conditions. No relations were observed between the prevalences of atopic diseases and maternal age at beginning of OC use, the duration of OC use, the type of contraceptive or maternal age at birth.

Conclusion: This study raises doubts in a true biological association between OC use and atopic diseases.

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The prevalence of asthma, allergic rhinitis and atopic eczema has increased worldwide over the last decades (1). Besides genetic factors the role of environmental and lifestyle-related factors in the development of asthma and atopic diseases is an important topic of current research (2–6). Especially early life exposures to allergens and infections seem to play a major role in the development of atopic diseases in later life (3, 4, 7, 8).

Recently, it has been suggested that maternal, genetic or environmental factors may even play a role before birth and lead to the subsequent development of atopic diseases (9–13). However, the contribution of these factors to the increasing trend in the prevalence of atopic diseases during the last three decades needs further investigation.

Wjst and Dold speculated about factors before gestation, namely maternal estrogen effects which might influence later atopy of the child (14). In an ecological study they reported an association between women's increased use of oral contraceptives (OC) beginning in the mid-1960s and the increasing prevalence of allergies. Xu et al. found a lower prevalence of atopy in children whose mothers reached menarche at a later age (15). They argued that age at menarche might be a marker of endogenous estrogen levels. However, these speculations are still not tested.

We used data of a cross-sectional survey to explore possible associations between maternal OC use and allergies in the offspring of East German school children.

Methods

Subjects and materials

Between 1998 and 1999, 2754 pre- and elementary school children aged 5–14 years were recruited from communities of Bitterfeld, Hettstedt, and Zerbst. Teachers distributed questionnaires to the children's parents. The overall response rate was 75.9%. All children who consented to participate in the study underwent physical examinations at their schools and had blood drawn. The blood was immediately frozen and stored at –20°C, and the same laboratory analyzed all samples in 1999. A detailed description of the study design and the survey population has previously been published (16, 17).

Immunologic assays

Allergic sensitization to common aeroallergens (house dust mite *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, cat mixed grasses, and birch pollen) was assessed by specific serum immunoglobulin E (IgE) measurements, using radioallergosorbent test (RAST).

Questionnaire

We considered the following health outcomes from the questionnaire: ever physician-diagnosed allergic diseases (asthma, hay fever, and atopic eczema), and parental reported allergic symptoms (ever wheezing, rhinitis symptoms in the past 12 months, and ever itchy rash). We combined children with at least one of the symptoms

frequent sneezing, runny or blocked nose without concurrent infection and itchy eyes in the group rhinitis symptoms.

Children were divided into the groups OC use after birth and OC use before birth using the calculated age of the mother at the time of the birth of her child and the age of the mother starting OC use. The following information and questions were used for the analyses:

- Date of birth of mother and child
- Has the mother of the child ever taken OC?
- At what age did the mother of the child start with the OC use?
- When was the OC use stopped before the pregnancy with the child?
- How many years were OC taken before the pregnancy with this child?
- Name of the OC that was taken?

Statistical methods

We employed logistic regression models for dichotomous and ordinal outcome variables. All computations were performed using the statistical analysis package SAS for Windows version 8.1 (SAS Institute, Cary, NC, USA).

Results

Of the 2754 children in the study information of maternal OC use was available for 2405 children. Additionally 2314 mothers provided information about the time of OC use; 1686 mothers had used OC before the birth of the child, 130 mothers started OC use after the birth of the children and 498 children lived in families where the mother had never used OC.

The crude prevalence of atopic diseases and atopic symptoms in children without maternal OC use and maternal OC use before and after birth are summarized in Table 1.

Table 1. Crude prevalence of atopic diseases and atopic symptoms in East German children aged 5–14 years with no maternal use of oral contraceptives and children with maternal contraceptive use before and after birth, 1998–99

	OC use		
	Never (%) <i>n</i> = 498	Before birth (%) <i>n</i> = 1686	After birth (%) <i>n</i> = 130
Asthma*, †	4.4	5.6	7.1
Wheezing (ever) ‡	16.9	22.9	21.8
Atopic rhinitis*	6.6	10.3	10.3
Runny or blocked nose without infection and itchy eyes ‡, §	1.8	2.6	1.5
Atopic eczema*	4.1	10.5	12.5
Itchy rash or itchy skin (ever) ‡	12.6	21.8	22.0
Sensitization¶			
RAST > 0 (>0.35 kU/l)	23.7	26.1	25.4
RAST > 1 (>0.7 kU/l)	20.1	22.2	23.1
RAST > 2 (>3.5 kU/l)	11.4	14.9	13.8
RAST > 3 (>17.5 kU/l)	6.8	9.9	10.0

* Doctoral diagnoses.

† Asthma or asthmatic bronchitis.

‡ Parental reported allergic symptoms.

§ During the last 12 months.

¶ At least one specific IgE against grass pollen, birch pollen, cat, *Dermatophagoides pteronyssinus* or *cladosporium* (RAST-FEIA-CAP).

Parents in the groups with maternal OC use before and after the birth of the child differ from those without OC use in some respects. The characteristics of possible confounders are presented in Table 2.

The adjusted results presented in Fig. 1 show that maternal OC use before birth was associated with a higher risk of asthma [odds ratio (OR) 1.6; 95% confidence interval (CI): 0.9–3.0], allergic rhinitis (OR 1.5; CI: 0.96–2.2), atopic eczema (OR 2.6; CI: 1.6–4.3) and atopic sensitization (OR 1.5; CI: 0.97–2.2) in the offspring. Similar effect estimates were found for OC use exclusively after the birth of the child.

Table 2. Characteristics of possible confounders in East German children aged 5–14 years whose mother had never used oral contraceptives and whose mothers had used oral contraceptives before and after birth, 1998–99

	OC use		
	Never (%) <i>n</i> = 498	Before birth (%) <i>n</i> = 1686	After birth (%) <i>n</i> = 130
Age			
5–7 years	19.3	14.3	9.2
8–10 years	35.1	35.7	30.8
11–14 years	45.6	50.0	60.0
Sex: boys	54.4	53.0	53.9
High parental education*	35.3	42.9	28.4
Parental atopy†	25.3	35.2	35.4
Mother's age at birth of the child (mean)	25.6	25.2	21.4
Maternal smoking during pregnancy	12.5	7.4	13.9
Preterm birth	9.5	7.1	6.2
≥4 weeks breast feeding	46.9	49.5	43.4
No siblings	23.7	26.2	33.9
Bedroom sharing	42.8	30.1	41.5
Day nursery (<1 year)	61.4	81.5	79.8

* Parental education ≥12 years.

† Father or mother having asthma, hay fever, eczema or other allergies.

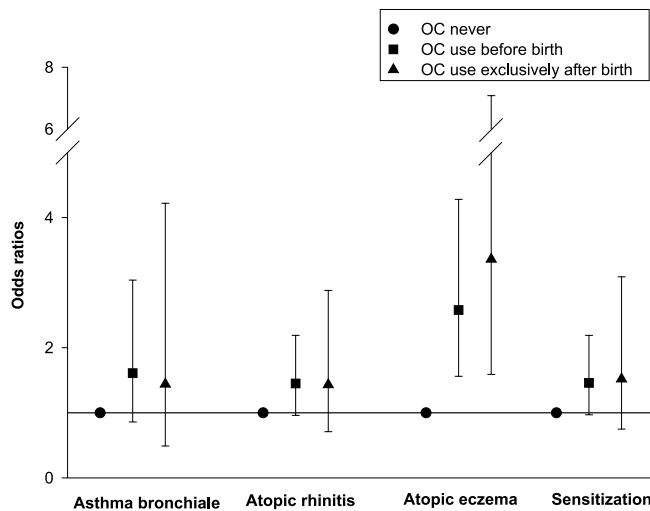


Figure 1. Adjusted odds ratios of asthma, atopic dermatitis, atopic eczema and atopic sensitization in East German children aged 5–14 years whose mother had used OC before or exclusively after birth compared with children whose mothers had never used OC, 1998–99. Outcomes were adjusted for age, gender, area, parental education, and parental atopy. Vertical bars indicate 95% confidence intervals.

Further adjustment for the factors mother's age at birth of the child, maternal smoking during pregnancy, preterm birth, ≥ 4 weeks exclusively breast feeding, siblings, bedroom sharing, day nursery (< 1 year) did not change these results (data not shown). We found no association between the duration of maternal OC use before birth and later atopic diseases in the offspring. Additional sensitivity analyses exploring maternal age at birth, maternal age at beginning of OC use, time between the stop of OC use and conception or the type of contraceptive showed no associations with atopic diseases in the children, either (data not shown).

Discussion

Oral contraceptives and atopic diseases in the offspring

There are only two studies that investigated an association between contraceptive use and atopic diseases in the offspring. Xu et al. investigated prenatal factors and the occurrence of rhinitis and eczema among offspring in a population-based cohort with more than 8000 Finnish children and found a slightly higher risk for allergic eczema in mothers who used the pill before pregnancy compared with women who had not used contraceptives before pregnancy (18).

Peters and Golding reported an increased risk of childhood eczema for children of mothers who used OC in the 18 months prior to pregnancy in a cohort of 10 900 5-year-old children (19).

Summarizing the results of the few studies there seems to be a slightly higher risk for atopic diseases in the offspring of OC users supporting the speculations of Wjst et al. (1997). Wjst suggested several hypotheses of semiacute, indirect and chronic effects to explain the lag effect between successful contraception and later gestation of an atopic child (14). To our knowledge the association of OC use before and after birth and atopic diseases has not been analyzed yet. At first glance at the association of children of mothers with maternal OC use before birth compared with children whose mothers had never taken OC there is an increased risk between maternal OC use and asthma, allergic rhinitis and atopic eczema. But if maternal OC use is truly responsible for later atopy of the offspring, OC have to be taken *before* the birth of the child. Our findings that OC use *after* the birth of the child is associated with atopic diseases, too, raises major doubts of a true association. It seems much more likely that OC use is confounded strongly with an unknown factor that is responsible for the higher risk of atopy. Further support for these doubt comes from the two studies that reported association between OC and atopic diseases in the offspring as other contraceptive methods like intrauterine devices showed a higher risk for atopic diseases as well (18, 19).

Our data comprised a great number of known and speculative confounders for allergic manifestations like parental education, parental atopy, number of siblings, maternal smoking during pregnancy, preterm birth, breast feeding, day nursery, and bedroom sharing but adjustment for these possible confounders changed the results only marginally. A possible exposure to OC after birth could be through breast milk. About 30% of the children were breastfed for 4–12 weeks and 20% for more than 12 weeks. Like all drugs taken by breastfeeding mothers, small amounts of OC can be transferred to the infant via breast milk. But the amounts are small and only very few women start with OC during breastfeeding. Nevertheless, it seems possible that OC transmitted by breast feeding may have an impact on later atopic diseases of the child. This remains to be investigated. In summary, we do not have clear evidence, as to which factor is responsible for our results.

Methodological issues

In a cross-sectional study the issue of recall bias has to be addressed. As there is no major public interest about OC use and atopic diseases, recall bias seems unlikely. Also, the results are very similar for asthma, allergic rhinitis, atopic eczema, and allergic sensitization.

A limitation of our study is the retrospective assessment of OC use before and after birth. Oral contraceptives can only be obtained by prescription from a doctor in East Germany. In addition contraception and family planning are important issues so that women probably

remember whether and when they used OC. A second possible limitation of our study is that parental questionnaire data were used. However, the questionnaire results (doctoral diagnosis of asthma, allergic rhinitis, and atopic eczema) show a similarity with objective parameters like atopic sensitizations.

In a cross-sectional survey it is impossible to answer the question of causal relationships. Our analyses however, with the finding that OC use is associated with atopic diseases regardless of whether OC were taken before or after birth of the child make it unlikely that there is a true biologic mechanism. We rather believe that the association is caused by confounding or that OC use is a proxy for social, environmental or even genetic differences that is unknown so far. Thus our study emphasizes the

possible flaws in cross-sectional studies and the importance of a careful interpretation of results from cross-sectional studies.

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