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Interpregnancy interval might affect the risk of childhood atopy

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To the Editor:

Despite the great effect of atopy on children's health, factors affecting the risk of childhood atopy are not well understood, and causes are still being sought. The early life environment, including the in utero environment, might be particularly important in modulating the later risk of atopy.[1] Numerous studies suggest that larger family size and higher birth order are related to a decreased risk of childhood atopy or related symptoms.[2] Despite this consistent finding, only 2 studies have examined the interval between pregnancies as a potential risk factor for childhood atopy, and the results are in conflict.[3,4] The interpregnancy interval has recently been found to be a major risk factor for preeclampsia,[5,6] a condition believed to be related to immune factors during pregnancy. We examined the association between the length of the interpregnancy interval and childhood atopy status as determined by skin testing in a birth cohort of children ages 6 to 7 years in the Detroit, Michigan, area.

This analysis used data from the Childhood Allergy Study (CAS), which was conducted among children in the Health Alliance Plan (HAP), a health maintenance organization in the Detroit, Michigan, area. We calculated the interpregnancy interval as the birth date of the study subject minus the birth date of the next oldest sibling and examined its relationship to atopy at age 6 to 7 years.

Briefly, the CAS is an ongoing study to evaluate the environmental determinants of pediatric allergy and asthma. All women at least 18 years of age living in a predefined geographic area who had an estimated date of confinement between April 15, 1987, and August 31, 1989, and who were members of the HAP and planned to deliver at the hospitals covered by the HAP were eligible for the study and were invited to participate. Only full-term infants (≥36 weeks gestation) were included in the study. Further details have been previously published.[7] The institutional review board at Henry Ford Health System approved the original study, and informed consent was obtained each time information was collected.

Of the 1194 women who were eligible for the CAS study, 953 (80%) consented to participate. In the case of multiple births, a single child was chosen randomly for the study. Infants from 106 (11%) of these women were not further enrolled in the study because their cord blood was not collected at delivery (a requirement of the original protocol). Of the remaining 847 (89%) infants, 6 had cord blood that was believed to be contaminated, and 6 more were determined to be ineligible at subsequent review of eligibility criteria. Four hundred eighty-four (57%) of the 835 children underwent a clinical evaluation for allergic sensitization and asthma between ages 6 and 7 years. Those who underwent clinical evaluation were not different from those who did not with respect to parental allergy and asthma history, the presence of cats and dogs in the house, and parental education.[8] Of the 484 children, we had complete information on

prior pregnancies, live births, and sibling ages for 419 (87%) children from prenatal and subsequent interviews with the mothers (96% were white).

At the clinical examination, children underwent skin prick tests for *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, ragweed (*Ambrosia artemisiifolia*), cat, bluegrass (*Poa pratensis*), and *Alternaria* species (extracts from Bayer Biologics, Spokane, Wash). Both positive (histamine, 1 mg/mL) and negative (glycerosaline) controls were used. Tests were applied by using the puncture method with a lancet (Bayer Biologics). A positive test result was defined as a wheal of 2 × 2 mm or larger with a flare larger than the wheal. If subjects had one or more positive skin test responses, they were classified as atopic (30% of the children examined).

We had complete information on atopy from 415 of the 419 children. Interpregnancy interval group cutoff points were chosen by pairing adjacent 1-year intervals to create sufficient numbers in the strata. Because of small numbers, we grouped interpregnancy intervals of 5 or more years. Cutoff points were chosen before examining associations.

We used risk models (SAS 8.0) to quantify the associations between interpregnancy interval categories and atopy status. Because of the small numbers, we were not able to evaluate potential effect modifiers.

Of the 415 women, 135 (32%) had no prior pregnancies, 48 (11%) had prior pregnancies but no prior live births, 92 (22%) had an interpregnancy interval of less than 2 years, 90 (22%) had an interpregnancy interval of 3 to 4 years, and 50 (12%) had an interpregnancy interval of at least 5 years. Table I presents unadjusted and adjusted relative risks of atopy for different interpregnancy intervals compared with births that did not follow any prior pregnancy. Children born to women who reported a prior pregnancy but no prior live births were assigned their own group. Children born after interpregnancy intervals of less than 2 years were far less likely to have positive test results for atopy compared with children of women who had no prior pregnancies (adjusted relative risk, 0.46; 95% CI, 0.24–0.92). We included parental history of allergies (mother or father given a diagnosis by a doctor) and pet exposure (none, 1, ≥2 pets in the household) in the adjusted model because they were associated with the risk of atopy at a *P* value of less than .10, although neither were confounders. Although the number of prior live births was neither predictive of atopy nor a confounder of the association between interpregnancy interval and atopy, we included it in the adjusted model because of its prominent role in the allergy risk factor literature (adjusted relative risk, 1.11; 95% CI, 0.82–1.51 for a difference of 1 prior live birth). The association with interpregnancy interval was not appreciably confounded by the child's sex, maternal-only history of allergies, maternal smoking during pregnancy (yes or no), childcare use (any time in childcare before age 1 year), or season of birth. We had no information on infection or nutrition during pregnancy.

Two previous studies have examined the interpregnancy interval. Strachan et al[3] found no association between the interpregnancy interval dichotomized at 3 years and physician-diagnosed hay fever or positive skin prick test responses to grass pollen. Other allergens were not tested. Ponsonby et al[4] found that among the youngest children in a family, the shortest interpregnancy interval (0–2 years) was associated with a lower rate of parental report of hay fever in their child at age 7 years. No skin test data were presented.

Recent research on preeclampsia, a condition in pregnancy believed to be mediated by maternal immune status, has found a protective effect of prior pregnancies.[5,6] In large studies of Danish women[5] and Norwegian women,[6] pregnancies after a shorter interpregnancy interval were found to be at reduced risk for preeclampsia compared with pregnancies after longer interpregnancy intervals. In the Norwegian cohort the effect was not linear, and the risk for preeclampsia at more than 10 years after a pregnancy was similar to the risk experienced by

women who had never been pregnant. The publication of these data was not accompanied by speculation about possible mechanisms. However, the role of the interpregnancy interval in the cause of preeclampsia suggests that it might play a role in modulating immunologic factors in pregnancy.

Our finding might be related to the hygiene hypothesis (ie, factors associated with childhood infection are associated with atopy), which has been proposed to explain the protective effect of larger family size and later birth order on atopy.[3] For example, children born after a shorter interpregnancy interval might be more likely to play with their siblings and thus have greater opportunity to share infections. Perhaps the time demands of closely spaced children leave their parents with less time to maintain the same standards of cleanliness as parents in homes in which children are further apart in age.

Alternatively, a woman's immunologic profile might alter her fertility, as reflected in her interpregnancy interval. Sunyer et al[9] found that maternal atopy, as determined by means of skin prick testing (some women tested in the first trimester, some in the third trimester, and some 6 months postpartum), was inversely related to the number of offspring. This finding persisted across 3 separate cohorts of women (1 from the United Kingdom and 2 from Spain). The authors speculated that atopy might reduce fertility or that pregnancy might have a permanent immunosuppressive effect on the mother. They did not look at the interpregnancy interval. However, if the effect they observed was due to immunosuppressive effects of prior pregnancies, then it is possible that the spacing of pregnancies might also be important. Perhaps closely spaced pregnancies allow less time for recovery from any immunosuppressive effect of previous pregnancies.

Finally, prior pregnancies and their spacing might influence the in utero environment. It has been suggested that in utero priming of the immune system modulates the later risk of atopic illness in the child.[1] In addition to the number of prior pregnancies, the interval between pregnancies might alter the in utero immunologic milieu in ways that affect the risk of atopy in the child.

A successful pregnancy is a fine balance between a mother's tolerance for her fetus's foreign genetic material and the fetus's ability to survive the mother's immunologic defenses. Understanding the mechanism by which the interpregnancy interval might affect atopic status in the offspring will require filling in many gaps in research. Delineating the changes in a woman's immune function during pregnancy is an area of active research, but there are few concrete data at present.[10] Furthermore, describing the biologic effects of the interpregnancy interval would require a better understanding of whether and how the mother's immune system influences fetal immune function and the offspring's immune development after birth.

These results must be regarded as preliminary given the size of the study. However, our data suggest that it might be worthwhile to look not only at birth order and number of siblings but to also consider the role of pregnancy history in a child's risk of atopy. A detailed pregnancy history from the mothers, including the specific outcomes and timing of all prior pregnancies, takes but a few minutes to collect and might provide insight into the relationship between family size, family composition, and the risk of atopy.

References

1. Holt PG. Programming for responsiveness to environmental antigens that trigger allergic respiratory disease in adulthood is initiated during the perinatal period. Environ Health Perspect 1998;106(suppl 3):795–800. [PubMed: 9646039]

2. Karmaus W, Arshad H, Mattes J. Does the sibling effect have its origin in utero? Investigating birth order, cord blood immunoglobulin E concentration, and allergic sensitization at age 4 years. Am J Epidemiol 2001;154:909–15. [PubMed: 11700245]

3. Strachan DP, Taylor EM, Carpenter RG. Family structure, neonatal infection, and hay fever in adolescence. Arch Dis Child 1996;74:422–6. [PubMed: 8669958]

4. Ponsonby AL, Couper D, Dwyer T, Carmichael A. Cross sectional study of the relation between sibling number and asthma, hay fever, and eczema. Arch Dis Child 1998;79:328–33. [PubMed: 9875043]

5. Basso O, Christensen K, Olsen J. Higher risk of pre-eclampsia after change of partner. An effect of longer interpregnancy intervals? Epidemiology 2001;12:624–9. [PubMed: 11679788]

6. Skjaerven R, Wilcox AJ, Lie RT. The interval between pregnancies and the risk of preeclampsia. N Engl J Med 2002;346:33–8. [PubMed: 11778000]

7. Ownby DR, Johnson CC, Peterson EL. Maternal smoking does not influence cord serum IgE or IgD concentrations. J Allergy Clin Immunol 1991;88:555–60. [PubMed: 1918722]

8. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. JAMA 2002;288:963–72. [PubMed: 12190366]

9. Sunyer J, Anto JM, Harris J, Torrent M, Vall O, Cullinan P, et al. Maternal atopy and parity. Clin Exp Allergy 2001;31:1352–5. [PubMed: 11591184]

10. Pearson H. Immunity's pregnant pause. Nature 2002;420:265–6. [PubMed: 12447413]

TABLE I

Relative risks and adjusted relative risks of atopy at age 6 years for different interpregnancy intervals, Childhood Asthma Study, Detroit, Mich, 1987–1993

Relative risk of atopy	No prior pregnancies	Prior pregnancies/no live births	Interpregnancy interval ≤2 y	Interpregnancy interval 3–4 y	Interpregnancy interval ≥5 y
Unadjusted	REF	0.92	0.57	0.83	0.72
95% CI		0.58–1.45	0.36–0.9	0.56–1.22	0.43–1.20
Adjusted*	REF	0.79	0.46	0.73	0.62
95% CI		0.45–1.38	0.24–0.92	0.41–1.30	0.28–1.38

REF, Referent category.

*Adjusted for childhood pet exposure, parental history of allergy, and number of prior live births.