

Parity and decreased use of oral contraceptives as predictors of asthma in young women

M. A. Jenkins*, S. C. Dharmage*, L. B. Flander*, J. A. Douglass†, A. M. Ugoni*, J. B. Carlin‡, S. M. Sawyer§, G. G. Giles¶ and J. L. Hopper*

*Department of Public Health, The University of Melbourne, Carlton, Vic. 3053, Australia, †Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Monash University, Melbourne, Vic. 3004, Australia, ‡Clinical Epidemiology and Biostatistics Unit, Royal Children's Hospital, Parkville, Vic. 3052, Australia, §Department of Paediatrics, Centre for Adolescent Health, Royal Children's Hospital, Murdoch Childrens Research Institute, The University of Melbourne, Parkville, Vic. 3052, Australia and ¶The Cancer Council Victoria, Carlton, Vic. 3053, Australia

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Summary

Background Asthma is more prevalent among males in childhood, but females report higher rates in adulthood. The reasons are unknown; although it has been hypothesized that hormonal factors may explain this sex-dependent risk of adult-onset asthma.

Objective To determine whether a woman's reproductive history or use of oral contraceptives is associated with adult-onset asthma.

Methods In 1991–1993, we surveyed 681 women aged 29–32 years randomly sampled from participants first surveyed at age 7 years by the 1968 Tasmanian Asthma Survey, a study of all children born in 1961 and attending school. Current asthma was defined as reporting asthma or wheezy breathing in the past 12 months.

Results In women who did not have asthma or wheezy breathing by age 7 years, 13% had current asthma. The risk of current asthma in these who were parous increased with the number of births (odds ratio (OR) 1.50 per birth, 95% confidence interval (CI) 1.01–2.23 $P = 0.04$) while women with one birth were at a lower risk than nulliparous women (OR 0.46 95% CI 0.2–1.06, $P = 0.07$). Independent of parity, the risk decreased by 7% (95% CI 0–13%) per year of oral contraceptive pill use in all women. In women who did have asthma or wheezy breathing by age 7 years, neither reproductive history nor oral contraceptive pill use predicted current asthma.

Conclusion Our observation that parity and decreased oral contraceptive use predict asthma in women, is consistent with the hypothesis that the asthma that develops after childhood is in part a response to endogenous and exogenous female hormones. This may be due to alterations of cytokine responses by the pregnant state, triggering adult-onset asthma in women.

Keywords adult-onset asthma, hormones, oral contraceptive use, pregnancy

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Correspondence:

Mark A. Jenkins, Centre for Molecular, Environmental, Genetic and Analytical Epidemiology, Department of Public Health, The University of Melbourne, Level 2, 723 Swanston Street, Carlton, Vic. 3053, Australia.
E-mail: mjenkins@unimelb.edu.au

Introduction

Retrospective and prospective questionnaire studies have shown that the incidence of asthma differs by sex with age, being higher in males during childhood, about the same in both sexes during teenage years, but higher in females during adulthood [1, 2]. Asthma severity, as measured by hospital admissions, also appears to follow the same sex-by-age-dependent pattern [3, 4].

Several explanations have been hypothesized to explain this phenomenon including sex differences in

hormonal changes, size of the airways, rate of lung growth, perception and management of asthma symptoms and environmental exposures [5–8]. Evidence for a role of hormonal factors on asthma in women comes mainly from clinical research on small numbers of subjects and animal studies. There do not appear to be any prospective, population-based epidemiological studies that have examined whether these factors are associated with asthma onset in adulthood and, if so, to what degree. We have previously shown that three of every four children with

asthma by age 7 years will not have asthma as an adult and only one in three adults with asthma had asthma by age 7 years [9], suggesting the existence of risk factors acting during late childhood, adolescence and/or early adulthood on adult-onset disease.

In this paper, we have used a 25-year follow-up of a random sample of women, initially surveyed as children in 1968 as part of a large population survey of all Tasmanian schoolchildren born in 1961 [9], to assess prospectively if asthma developing since age 7 years is predicted by a woman's reproductive history or use of oral contraceptives.

Materials and methods

Study subjects

In 1968, for all 8683 children born in 1961 and attending school in Tasmania, Australia, (the cohort), parents were asked to complete questionnaires on their children's history of respiratory symptoms including asthma. For the girls, responses were obtained for 4193 (99%). The administration, methodology, questionnaires, and results have been previously reported [10, 11]. Cohort members were classified as having 'asthma by age 7 years' if parents answered yes to the question: 'Has he/she at any time in his/her life suffered from attacks of asthma or wheezy breathing? (Note: Please regard 'asthma' and 'wheezy breathing' as being much the same thing for this survey; we do not ask you to try to tell the difference)'.

During 1991–1993 a stratified random sample of 2000 male and female cohort members, half with asthma by age 7 years (as reported by the parents in the 1968 survey) were surveyed using a mailed self-completed questionnaire 'The Tasmanian Long-Term Health Survey' [9]. The questionnaire contained the same question on asthma or wheezy breathing as used in the 1968 survey as well as questions on frequency and onset of asthma attacks. The study was approved by the Ethics Committee on Research at the Royal Melbourne Hospital. Responses were obtained from 681 of the 896 selected females (76%), independent of asthma status by age 7 years (75% vs. 77%).

Data

The outcome variable, current asthma, was defined as asthma or wheezy breathing in the last 12 months measured by the 1991–1993 questionnaire. Self-report of current asthma, as compared with a physician's diagnosis of current asthma after consultation with a subject, has a sensitivity of 80% and a specificity of 97% [12].

In addition to asthma by age 7 years as reported by their parents in the 1968 survey (yes, no), covariates relevant to this analysis addressed by the 1991–1993 questionnaire were duration of oral contraceptive pill use (years); parous

(yes, no); age at birth of first child (years); total number of births (number); past history of smoking (yes, no); current smoking status (smoker, non-smoker); and number of years of secondary school completed (years).

Statistical analysis

The associations between current asthma and parity, oral contraceptive use and potential confounders were initially examined using χ^2 tests and then by computing univariate odds ratios and 95% confidence intervals (CIs) using simple logistic regression. Multiple logistic regression was used to analyse risk of current asthma as a function of all the covariates described. Modelling was performed separately for women reported to have, or not have asthma by age 7 years. For parity variables, covariates were a two-level factor for ever having had a child; a linear effect for subsequent births ('number of births minus 1' for parous women or zero in nulliparous women); and a linear effect for age at first birth (or 32 in nulliparous women). In this way, the model fitted a linear effect with parity for values of parity greater than zero (and for time since last birth), but allowed a separate estimate for the odds of asthma at zero parity. Education and smoking status were examined as potential confounders. A change in the estimates of 15% or more, or a likelihood ratio test *P*-value of 0.1 or less, was regarded as indicating important confounding. Stata [13] was used in all the analyses.

Results

The prevalence of current asthma among females who did not have asthma by age 7 years was 13% and among those who did have asthma by age seven was 29%. The distribution of the number of births and oral contraceptive use in the total sample is described in Table 1. Seventy-one per cent of the women had had at least one birth and 78% had used oral contraceptives for more than 3 years over their life-time.

Table 1 shows the prevalence of current asthma in women who did not have asthma by age 7 years increased from 8% for one birth to 29% for four or more births (*P* = 0.031). This is despite the prevalence of current asthma in parous women overall being marginally lower (12.6%), although not statistically significantly so, than in non-parous women (15%). The prevalence of current asthma in the same group of women decreased with the number of years of oral contraceptive pill use, from 20% in women with less than 4 years use to 6% for women with 12 or more years use (*P* = 0.007).

Neither education nor smoking confounded the association between parity, oral contraceptive use and prevalence of current asthma. In a multivariable model that included number of births as a two-level factor (with an

Table 1. Distribution of women, proportion (%) and proportion (%) with current asthma by parity, age at first birth, oral contraceptive use, smoking and education, stratified by all women, women who did not have asthma by age 7 years and women who did have asthma by age 7 years

Characteristics	Number of women (percentage of all women in the category)	Number of women (percentage with current asthma)	
		No asthma by age 7 years	Asthma by age 7 years
All females	681 (100)	388 (13)	293 (29)
Number of births			
0	196 (29)	111 (15)	85 (25)
1	119 (18)	72 (8)	47 (25)
2	232 (34)	129 (11)	103 (33)
3	101 (15)	62 (17)	39 (38)
4 or more	33 (5)	14 (29)	19 (26)
Years of oral contraceptive pill use			
0–3	154 (23)	88 (20)	66 (29)
4–7	223 (33)	120 (12)	103 (28)
8–11	168 (25)	99 (14)	69 (30)
12 or more	136 (20)	81 (6)	55 (33)
Smoking history			
Current	225 (33)	127 (17)	98 (26)
Past	190 (28)	111 (11)	79 (32)
Never	266 (39)	150 (12)	116 (30)
Years of high school			
0–3	97 (14)	48 (19)	49 (22)
4–6	584 (88)	340 (13)	244 (31)
Parous females	485 (71)	277 (13)	208 (32)
Age at birth of first child			
< 20	67 (10)	33 (12)	34 (26)
20–23	142 (21)	75 (19)	67 (34)
24–27	157 (23)	99 (7)	58 (43)
28 or over	95 (14)	58 (7)	37 (16)
Unknown	24 (4)	12 (50)	12 (25)

effect for ever having had a child and a linear effect for subsequent birth number in those with at least one); oral contraceptive use and education, the risk of current asthma increased for each birth (odds ratio 1.50; 95% confidence interval 1.03–2.23 $P=0.04$). The difference between the risks of current asthma in women with one birth vs. women with no births was of marginal significance (OR 0.46 95% CI 0.2–1.06 $P=0.07$). Independent of parity, the risk decreased by 7% (OR 0.93%, 95% CI 0.87–1.0 $P=0.05$) for each year of oral contraceptive pill use in all women. A sensitivity analysis was conducted by excluding those who developed current asthma before age 14 and the results were similar (not shown).

Figure 1 displays the predicted proportions of women with current asthma that were computed using the estimates of the multivariable regression model. Under this model, in women who have not used oral contraceptives,

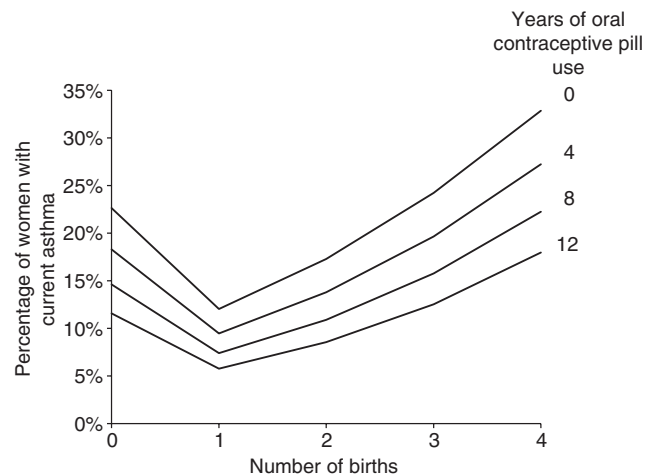


Fig. 1. Predicted proportions (%) of women with current asthma in the last 12 months in women who did not have asthma by age seven, by number of births and years of oral contraceptive pill use.

the risk of asthma is estimated to increase, on average, from about 13% if they have had one birth to 33% if they have had four births. In contrast, for women who had used oral contraceptives for 12 years the corresponding estimated average increase in risk is from 6% to 17%.

In women who had asthma by age seven, none of the covariates was significantly associated with current asthma (all $P > 0.05$).

Discussion

We have previously shown, using the same cohort, that 29–32 year-old women without asthma by age seven were almost twice as likely as men to have current asthma [9]. In this study, we examined possible female-specific risk factors for adult asthma, and found some evidence that the risk of later-onset asthma among women who had no asthma by age seven was associated with increased parity, following a decreased risk from the first birth, and decreased oral contraceptive pill use. This is the first cohort, to our knowledge, in which an association between parity and adult-onset asthma in women has been reported. Our findings suggest that the hormonal influences of pregnancy and oral contraceptive use may play a role in the genesis of adult-onset asthma in women.

The Tasmanian cohort, on which this study is based, is one of the first population-based asthma cohort studies to be established and is consequently the first to report on associations between pregnancy history and asthma prevalence. The prospective data acquisition of this study enabled comparison of the childhood asthma status recalled by the subjects when adults with their childhood asthma status reported at the time by their parents. If, in this analysis, we had relied on recall, as retrospective studies must do, approximately two-thirds of women who

had asthma by age seven (according to their parents at the time) would have been wrongly classified as not having had asthma by age seven, as they either reported never having asthma or having asthma only after age 7 years [9]. Such misclassification would result in reduced power to observe any associations between risk factors and adult-onset asthma.

A limitation of this study is the lack of immunological data, such as skin test sensitivities and tests of lymphocyte function in adulthood, which may have provided an explanation for our observations. Notwithstanding, the cohort was established in a large, representative population in a single state of Australia with remarkably high participation rates at the fourth cycle of the study.

Several explanations seem possible for the observed associations between asthma risk and parity and oral contraceptive pill. These include inadequate control of confounding, in particular perhaps with socio-economic status. However, these associations were not observed for women with a history of childhood asthma. Furthermore, in multivariable modelling, the association between number of births or age at birth of first child was not altered by adjusting for years of secondary school completed (a proxy measure related to socio-economic status), suggesting that neither confounding nor socio-economic status are likely explanations.

Another theory for the sex difference in asthma rates is that women may with children may have a greater exposure to household environmental agents known to trigger asthma, such as viral infections [14], and nitrogen oxides which are produced in cooking and heating [7]. However, this does not explain why only women who did not have asthma as a child were at increased risk of asthma with an increasing number of births.

An intriguing explanation for the observed change in asthma prevalence is that the hormonal changes of pregnancy or prolonged oral contraceptive pill use may invoke durable and cumulative changes on the immune system, leading to asthma. The immunological genesis of asthma involves the secretion of cytokines such as IL-4 and IL-5 by lymphocytes with a predominant Th2 phenotype [15, 16]. The non-atopic adult immune system is characterized by a relative T-helper type 1 (Th1) lymphocyte predominance. During pregnancy, however, an immunological state of tolerance to the fetus is invoked with suppression of the Th1 cells and the promotion of a Th2 cell dominance [17, 18]. Production of cytokines such as IL-4 and IL-10 may result in protection of the fetus by immune suppression of the mother and, we postulate, may also increase the risk of subsequent allergic responses in the mother. This pathway may involve production of the female hormones progesterone, prostaglandin E, and relaxin during pregnancy which have been shown to favour elevated maternal levels of Th2 cytokines [19,20]. Women who had allergic asthma as a child may maintain

a predominance of Th2 cells into adulthood which would be unaffected by the immunological consequences of pregnancy. In contrast, women who did not have allergic asthma during childhood are more like to have Th1 lymphocyte predominance that could be subject to reversal with pregnancy. However, the conjecture above does not explain the observed apparent decrease in asthma following the first birth and subsequent increasing asthma risk with additional births.

The inverse association between oral contraceptive pill use and current asthma may be expected if, over time, this exposure results in a change in lymphocyte cytokine production that mimics the never-pregnant state or masks the effect of pregnancies on Th2 cytokines. The association is also consistent with reports that premenstrual aggravation of asthma, which occurs in up to 40% of asthmatic women, may be due to the rise in progesterone and estradiol levels in the luteal phase [8]. Studies on lung tissue in animals demonstrate that an increase in estradiol levels results in an increase in sympathetic and parasympathetic receptor densities in the lung [21, 22]. Use of oral contraceptives has been found to suppress the luteal phase rise in sex hormones and to attenuate the airway reactivity of asthmatics [8]. This suppression over time may inhibit progress towards asthma.

In summary our data suggest that in women there may be an association between parity, oral contraceptive use and risk of later-onset asthma (after the age of 7 years). Prospective clinical studies of T cell levels, atopy, and asthma symptoms before and after successive pregnancies may be needed to further investigate these relationships.

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