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Original article

Why do studies show different associations between intrauterine exposure to maternal smoking and age at menarche?

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ABSTRACT

Purpose: Studies suggests that intrauterine exposure to maternal smoking both accelerates or delays age at menarche. We hypothesize that these opposing findings relate to different infant and childhood growth patterns across cohorts.
Methods: Using data from an adult follow-up study of the Child Health and Development Studies and the National Collaborative Perinatal Project, we examined, using generalized estimating linear regression models, whether intrauterine exposure to maternal smoking was associated with age at menarche in 1090 daughters before and after accounting for growth in weight.
Results: Compared to the nonexposed, intrauterine exposure to maternal smoking was associated with a 4-month acceleration in menarche in the National Collaborative Perinatal Project ($\beta = -0.35$ years; 95% confidence interval [CI]: −0.63, −0.08), but a 6-month delay in menarche in the Child Health and Development Studies ($\beta = 0.48$ years; 95% CI: 0.13, 0.83), despite having a similar reduction in birth weight in both cohorts (~300 g). The results were more consistent across cohorts when we stratified by postnatal growth patterns. For example, in those with rapid weight gain (increasing two growth references from 0 to 4 years), intrauterine exposure to maternal smoking was related to a 7-month acceleration in menarche ($\beta = -0.56$ years; 95% CI: −0.95, −0.17).
Conclusions: These findings suggest that the association of intrauterine exposure to maternal smoking on age at menarche depends on postnatal growth patterns.

Introduction

The landmark 1965 United States Surgeon General's report that warned of the health hazards of smoking greatly reduced smoking prevalence in the United States. Although the percent of U.S. women currently smoking during pregnancy has declined dramatically in recent decades (12% in 2012 vs. 50% in 1965) [1], the question of whether intrauterine exposure to maternal smoking has additional health effects and can alter reproductive timing is still of public health concern because polycyclic aromatic hydrocarbons, compounds that are in cigarette smoke and other sources, are highly prevalent in our environment [2–4]. Examining the association between intrauterine exposure to maternal smoking and age at menarche is also of etiologic importance because early menarche is associated with increased breast cancer [5] and cardiovascular disease [6].

Several studies have examined whether intrauterine exposure to maternal smoking is associated with age at menarche with inconsistent results. Most studies find intrauterine exposure

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accelerates menarche [7–15], but others find it delays menarche [16,17], and some find no association [9,18]. While a recent meta-analysis concluded that intrauterine exposure is associated with accelerated menarche, it also reported strong heterogeneity across studies and highlighted the need to consider period-cohort effects and differences in socioeconomic status across the studies [19].

The fundamental concern when interpreting the existing epidemiologic literature is to disentangle whether the observed associations are caused by biological effects of maternal smoking exposure in utero or whether the association is being driven by noncausal factors. Given the associations of birth size, early life catch-up growth and prepubertal body size with the timing of menarche [20,21], it is important to consider these growth factors as possible mediators in the association between intrauterine exposure to maternal smoking and menarche. Intrauterine exposure to maternal smoking leads to small birth size in that on average maternal smoking causes a reduction in birth size of 200 g [1]. Being born small often leads to catch-up growth and because catch-up growth is associated with age at menarche, it may mediate the effect of intrauterine exposure to maternal smoking. However, given that babies born small have different rates of postnatal catch-up growth depending on their postnatal environment, it is important to investigate whether a plausible reason for opposing inferences on the role of intrauterine exposure to maternal smoking and age at menarche is because of different rates of catch–up growth across cohorts. Because smoke exposure, growth, and menarche are all socially patterned [22,23], it is also possible that socioeconomic status modifies the association of intrauterine exposure to maternal smoking on menarche.

Using data from two U.S. birth cohorts that prospectively collected information on intrauterine and postnatal exposure to maternal smoking, family socioeconomic status, and infant and childhood growth in the early 1960s, before the Surgeon General's report on smoking was released and less stigma was associated with reporting of smoking behavior, we examined the association between intrauterine exposure to maternal smoking and age at menarche after considering the possible confounding effects of maternal characteristics and the possible mediating and modifying effects of childhood growth patterns and socioeconomic status.

Material and methods

Study populations

We examined the associations of intrauterine exposure to maternal smoking with age at menarche in 1090 adult daughters participating in the Early Determinants of Mammographic Density (EDMD) Study [24]. The EDMD comprised subsets of two birth cohorts, the Child Health and Development Studies (CHDS) [25] and the National Collaborative Perinatal Project (NCPP) [26]. The association between intrauterine exposure to maternal smoking and age at menarche has previously been explored in other subsets of both these cohorts and show opposing effects [12,16,17]. Between 1959 and 1967, the CHDS was conducted in California and the NCPP was conducted in 12 sites across the United States. We used a subset of the CHDS and NCPP (Boston and Providence sites) based on adult daughters follow-up eligibility [24]. In brief, study criteria for the EDMD study were (1) singleton birth, (2) survived to last childhood follow-up, (3) birth size recorded at birth, (4) childhood growth measures for at least two time points, (5) third trimester serum available, and (6) at least one sister in the original cohort meeting the same criteria. Based on the EDMD study criteria, 3256 daughters in total, including 1163 sibling sets, were eligible [24]. We approached 1925 (59.1%) of the 3256 eligible daughters. We successfully traced 1314 daughters of which 1134 (86.3%) participated. Tracing rates were higher for the CHDS than for the NCPP (80.2% vs. 59.1%); however, participation rates were very similar once the women were successfully traced (85% and 88%, respectively). Of these, 1090 women (96.1% of the 1134 women) who had complete data on age at menarche were included in this study. The Institutional Review Boards at Columbia University Medical Center, Kaiser Permanente, Brigham and Women's Hospital and Brown University approved the EDMD study.

Baseline maternal data

The CHDS and NCPP cohorts enrolled pregnant mothers and followed them prospectively throughout their pregnancy. At the clinic visits, study staff collected information from mothers on prepregnancy body mass index (BMI), height, parity, family income, age at menarche, and ethnicity. At enrollment, mothers self-reported information regarding smoking during pregnancy. Mothers reported whether or not they smoked and if so, whether they smoked less than 1/2, 1/2 to less than 1, or greater than 1 pack per day.

Childhood growth data

At the time of delivery, birth weight and length was measured using standardized scales maintained by the studies. We assessed derived growth in height and weight measurements at 4 months, 1 year, and 4 years of age because these were the common time points when daughters were measured between the two cohorts. In the CHDS, serial growth measurements were abstracted from medical records [25]. In the NCPP, trained clinical staff measured childhood height and weight at 8 months or 12 months and at 4 years or 7 years of age [26]. Because the actual dates of the clinic visit differed for each individual and did not correspond to exactly 4 months, 1 year, and 4 years, we performed interpolations of height and weight measurements using individual cubic interpolation splines for each participant. We examined three patterns of weight change between birth and age 4 years based on Centers for Disease Control growth chart reference percentiles (fifth, 10th, 25th, 50th, 75th, and 95th): rapid weight gain defined children whose within-cohort percentile rank increased at least two major reference percentiles of weight from birth to 4 years of age; stable weight gain defined children whose rank stayed within two major percentiles; and slow weight gain defined children whose within-cohort percentile rank decreased at least two major percentiles.

Adult follow-up interview data

We interviewed adult daughters (aged 39–49 years) through a computer-assisted telephone interview. The interview included a question on “How old were you when you had your first menstrual period?” and responses were recorded in years and half years, for example, 13.5 years. Postnatal smoke exposure information was self-reported by the daughters in the adult follow-up questionnaire by asking “As a child, did any member of your household, including caregivers, smoke in your presence?”

Statistical analysis

We tested for differences between characteristics of the two cohorts within EDMD using χ^2 tests for categorical variables and t tests for continuous variables. We assessed the association between intrauterine exposure to maternal smoking and birth weight using mixed linear regression, adjusted for gestational age and maternal factors (race/ethnicity, prepregnancy BMI, height, and age at menarche).