Parental age at childbirth and age of menarche in the offspring

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BACKGROUND: Early age of menarche (AOM) is associated with serious health problems including breast cancer and heart disease. Rising parental age at childbirth is associated with some adverse health outcomes in the offspring, but whether early menarche is one of them is not known.

METHODS: We studied a Danish cohort of singleton females (n = 3168) born in 1984–1987. Prenatal data were collected from mothers around 36th week of pregnancy (self-administered questionnaire), although the menarcheal age was collected from daughters aged 17–21 years in 2005 (Web-based questionnaire). We assessed each parental age association in separate linear regression models adjusted for covariates (socioeconomic status, parity, maternal pre-pregnancy BMI, marital status, maternal smoking and daughter’s self-reported BMI), then included both ages in a third model.

RESULTS: Each year increase in maternal age showed a 9 day earlier onset of menarche in daughters [95% confidence interval (CI): −15.98, −2.90] and a 5 day earlier onset for each year increase in paternal age [95% CI: −10.85, 0.00], after adjusting for covariates. However, these associations attenuated when adjusted for the other parent [change in AOM in days: (i) maternal: −8.49 (95% CI: −17.09, 0.12), (ii) paternal: −1.14 (95% CI: −8.13, 5.84)].

CONCLUSIONS: We found no significant association between parental age and AOM, but the small sample of advance aged parents (over 30 years) limits the information we have. Future studies with a larger sample or a sample with over-representation of older parents will be of value.

Key words: age of menarche / maternal age / paternal age / parental age / early menarche

Introduction

Early age of menarche (AOM) has been associated with adverse health outcomes in adulthood, including increased risk for breast cancer, cardiovascular disease, elevated blood pressure, glucose intolerance, high allostatic load, increased mental distress, as well as early adoption of risky behaviors, such as alcohol use, smoking and early sexual debut (Allsworth et al., 2005; Deardorff et al., 2005; Remsberg et al., 2005; Lien et al., 2006; Ma et al., 2006a,b). If some of these associations are causal we need to identify potential causes and mechanisms of early AOM.

Since AOM has notably declined over time worldwide (Helm and Helm, 1984; Adadevoh et al., 1989; Papadimitriou et al. 1999; Olesen et al., 2000; Anderson et al., 2003; Do Lago et al., 2003; Silva and Padez, 2006)—much more than genetic factors alone can explain—this decrease must presumably have, at least in part, environmental causes. For example, in Denmark, the average AOM declined by 4 months from 13.40 to 13.03 years between 1965/1966 and 1982/1983, a 2.4 months drop in AOM per decade was reported in Brazil among a cohort of women born between 1931 and 1977, and in the USA an average drop in AOM by 2.5 months was observed between 1963–1970 and 1988–1994 with a further decline by 2.3 months in 1999–2002 (Helm and Helm, 1984; Anderson et al., 2003; Do Lago et al., 2003; Anderson and Must, 2005). Although the decline in timing of menarche over the past century was mainly attributed to improved socioeconomic status (SES), as reflected by better sanitation and nutrition, the ongoing declining secular trend in many developed countries suggests that causes other than socioeconomic changes must also exist (Zacharias and Wurtman, 1969; Marronan et al., 2000; Danubio et al., 2004; Anderson and Must, 2005; Aksglaede et al., 2009). In Denmark, although a few studies conducted in the 1980s and the early 1990s...
(Boldsen et al., 1993; Juul et al., 2006) reported a halt in the declining trend, a recent study reported a continual decline in menarcheal age (Aksglaede et al., 2009). These findings suggest that the secular trend of early AOM has not reached a stable age everywhere in the developed world and underscores the need to study potential causes other than socioeconomic factors for the ongoing declining AOM.

Currently, existing studies mainly focused on personal and demographic characteristics, such as obesity and social conditions, as the potential factors influencing the timing of menarche (Roberts et al., 1977; Adair, 2001; Adair and Gorden-Larsen, 2001; Freedman et al., 2002, 2003; Hesketh et al., 2002; Castelo-Branco et al., 2006; Ibanez et al., 2006; Opdahl et al., 2008). Only a few studies have examined exposures at the time of organogenesis, even though fetal programming of the timing of menarche is likely (Vatten et al., 2003; Windham et al., 2004; Axmon, 2006). The increasing trend of delayed childbearing may be one factor affecting prenatal programming. Age of parents has increased in many populations, especially in developed countries including Denmark (Heck et al., 1997; Council of Europe, 2004; Virtala et al., 2006; Charlton, 2007; Muganyizi and Kidanto, 2009).

Delayed maternal age is a well established risk factor for increased rate of chromosomal abnormalities resulting in genetic disorders in offspring (Hook et al., 1983; Hassold and Hunt, 2001; Pellistort et al., 2005). Growing evidence indicates that parental aging is also a risk factor for congenital malformations and genetic disorders (Newcombe and Tavendale, 1965; Savitz et al., 1991; Crow, 2000; Zhu et al., 2008), which may be linked to accumulation of mutations in germ cells of aging parents, perhaps resulting from normal wear and tear as well as exposure to harmful environments over time (Savitz et al., 1991; Yauk et al., 2007; Malik et al., 2008). Moreover, child bearing at a later age is associated with adverse birth outcomes, such as pre-eclampsia, pre-term birth, stillbirth, low birthweight and child mortality; and predisposition of the offspring to serious health problems such as autism, epilepsy, schizophrenia and Alzheimer’s disease (Fretts et al., 1995; Bertram et al., 1998; Abel et al., 2002; Harlap et al., 2002; Byrne et al., 2003; Astolfi et al., 2004, 2006; Vestergaard et al., 2005; Durkin et al., 2008; Zhu et al., 2008). Advanced maternal age at childbirth has been linked to menstrual disorders and subfertility in daughters owing to endocrinological irregularities (Smits et al., 1997). Studies on mice have shown that delayed parenthood, both maternal and paternal, reduces reproductive fitness, particularly among female offspring (Tarin et al., 2003; Garcia-Palomares et al., 2009).

These findings underscore the need to examine whether parental age at birth is also associated with the timing of menarche in female offspring. This study examines association between parental age at childbirth and timing of menarche, after adjusting for covariates. We hypothesize that older parents are more likely to have daughters with early onset of menarche.

Materials and Methods

Study design and data collection

This study used data from the Danish Aalborg Odense Birth Cohort (1984–1987). Three waves of data were collected, however, only the first and the last waves of data were used for this study. The first took place between April 1984 and April 1987 and included collection of data from mothers around the 36th week of pregnancy via self-administered questionnaires mailed to them as part of a health campaign ‘Health Habits for Two’ in Aalborg and Odense. Information was collected on pre- and post-conception health-related behaviors including exercise, nutrition, demographics, smoking and alcohol use. Information on paternal smoking, alcohol use and occupation were also included in the questionnaire sent to the mothers. In addition, birth outcomes and additional demographic information were collected from medical records at the end of their pregnancy. The cohort consisted of 11 144 singletons (5427 girls). Follow-ups were conducted in 2002 and 2005. In 2005, for the second data set, a follow-up Internet questionnaire was mailed to children of the cohort still alive and living in Denmark (n = 9811; 4669 girls). The questionnaire included information on children’s health and lifestyle, including sexual maturation. A total of 3382 girls (72%) answered the questionnaire and out of these, 3179 responded to the question on timing of menarche. Of them, ten had not reached menarche yet and one observation, whose child BMI value differed significantly from the rest, was excluded although it did not substantially change the outcome estimates. The remaining 3168 girls provided at least the year of their menarcheal onset with about half of them (1633) providing both the year and the month of menarche. Maternal and paternal ages at birth, calculated by subtracting the parental birthdates from the child’s birthdate provided in the medical form, were the two continuous independent variables. Covariates were selected based on literature review (Adair and Gorden-Larsen, 2001; Hesketh et al., 2002; Anderson et al., 2003; Do Lago et al., 2003; Windham et al., 2008; Kerm et al., 2009; Rubin et al., 2009) and DAGs (directed acyclic graph), and included SES based on both parents’ occupation (ranged from 0 to 2, with 0 being the highest SES which included at least one of the parents with the highest level of education or holding a job with large authority and 2 being the lowest SES which included unemployed, students or those holding jobs that did not require specific skills/training), marital status (0 = married, 1 = cohabited, 2 = single), maternal BMI before pregnancy, parity (0 = nulliparous, 1 = parous), maternal smoking during pregnancy (0 = never smoker, 1 = past smoker, 2 = smoked during pregnancy) and child’s BMI calculated from information provided during the follow-up in 2005. BMIs were calculated as: (weight in kilograms)/(height in meters)².

Analysis method

Since the data were based on women living in two different cities and their surrounding areas during pregnancy, the first step of the analysis involved testing for clustering effect at city level using the SAS proc mixed procedure. In absence of clustering effect, a series of multiple linear regression analyses was conducted with menarcheal age as outcome variable and parental ages at birth as independent variables adjusted for the covariates mentioned earlier. The initial regression analyses were restricted to the subset of the sample that provided complete menarcheal age information. First, the associations between each parental age and AOM were assessed separately adjusting for the covariates mentioned earlier. Next, age of both parents were mutually adjusted in the analysis to see if age of one parent was more important than age of the other parent: in order to draw comparisons, the latter model was replicated using the menarcheal age reported in years only. In addition, a multiple imputation analysis was conducted on a sample augmented by imputed values generated from the proc mixed procedure, which replaced missing values for all the variables in the model and the month of menarche. The method involved replacing the missing values with five imputed values based on the distribution of observed values. This created five complete datasets in which five regression analyses were carried out and the resulting regression coefficients were combined to produce mean coefficients (Rubin, 1987).
Regression diagnostic tests were conducted to ensure none of the model assumptions were violated and no statistical collinearity problems existed in the models. All statistical analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Parental characteristics and demographic distribution did not differ between the complete and the subset samples (n = 3168 and n = 1633). The maternal age at childbirth ranged from 15 to 48 years and fathers’ age ranged from 16 to 62 years, almost all (98%) were either married or cohabiting, and about half of the mothers (49%) were nulliparous. More girls were in the middle menarcheal age category (12–14 year) in the larger sample compared with the subset sample where more girls were in the oldest age category (>14 year, Table I). When compared with their younger counterparts, mothers and fathers who were 30 years or older at childbirth tended to be in the highest socio-economic stratum and were more likely to be never smokers. For example, 38% of mothers and 32% of fathers aged 30 years or older belonged to the highest socio-economic stratum versus only 10% of mothers and 7% of fathers aged 26 years or younger. Similarly, 62% of mothers and 58% of fathers in the oldest category reported never smoking compared with 46% fathers and 48% mothers in the youngest category (data not shown in table).

Scatter plots of parental ages against the menarcheal age did not show any clear pattern of association (figures not shown). But both paternal and maternal ages at birth of the child were negatively associated with menarcheal age of the child when assessed without adjusting for the second parent (Table II, model 0). AOM occurred 9 days earlier for each year increase in maternal age at childbirth [95% confidence interval (CI): −15.98, −2.90] and 5 days earlier for each year increase in paternal age [95% CI: −10.85, 0.00] for the subset of sample that provided both year and month of menarche. However, these associations were no longer significant at alpha level < 0.05 after adjusting for the second parent (Table II, Model 1) and the adjusted R² value was 0.03. The results from the larger sample with menarcheal age in years only and the sample with imputed data produced more attenuated associations, but in the same direction (Table II, Model 2 and 3).

Two interaction terms were initially included in the analysis to examine interactions between maternal and paternal ages at childbirth; and between paternal age and parity, but were later removed owing to their statistical non-significance (P = 0.62 and 0.16, respectively). Furthermore, none of the regression model assumptions were violated nor did any of the independent variables show strong collinearity problems (data not shown).

Table I Characteristics of parents and children included in study of parental age at childbirth and AOM in offspring.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subset of eligible participants</th>
<th>All eligible participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) Mean age (years) of menarche (SD)</td>
<td>n (%) Mean age (years) of menarche (SD)</td>
</tr>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) mean (SD)</td>
<td>27.8 (4.6)</td>
<td>27.7 (4.6)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 years old or younger</td>
<td>667 (40.9)</td>
<td>1352 (42.7)</td>
</tr>
<tr>
<td>27–29 years old</td>
<td>437 (26.8)</td>
<td>828 (26.2)</td>
</tr>
<tr>
<td>30–34 years old</td>
<td>384 (23.5)</td>
<td>725 (22.9)</td>
</tr>
<tr>
<td>Older than 34 years</td>
<td>144 (8.8)</td>
<td>261 (8.2)</td>
</tr>
<tr>
<td>Paternal characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) mean (SD)</td>
<td>30.4 (5.2)</td>
<td>30.3 (5.1)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 years old or younger</td>
<td>351 (22.0)</td>
<td>708 (22.9)</td>
</tr>
<tr>
<td>27–29 years old</td>
<td>403 (25.2)</td>
<td>767 (24.8)</td>
</tr>
<tr>
<td>30–34 years old</td>
<td>533 (33.3)</td>
<td>1019 (32.9)</td>
</tr>
<tr>
<td>older than 34 years</td>
<td>312 (19.5)</td>
<td>599 (19.4)</td>
</tr>
<tr>
<td>Child’s characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AOM (years) Mean (SD)</td>
<td>13.3 (1.4)</td>
<td>13.1 (1.4)</td>
</tr>
<tr>
<td>Categorical AOM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 year old</td>
<td>275 (16.8)</td>
<td>469 (14.8)</td>
</tr>
<tr>
<td>12–14 year old</td>
<td>919 (56.3)</td>
<td>2099 (66.3)</td>
</tr>
<tr>
<td>&gt;14 year old</td>
<td>439 (26.9)</td>
<td>600 (18.9)</td>
</tr>
</tbody>
</table>

Data are n (%) unless stated otherwise.

1 Subset of eligible participants includes only those who reported AOM in years and months. Eligible participants are those who provided their AOM at least in years.

2 The n values vary due to missing information on parental age at childbirth for some participants.
We found no significant association between advanced parental age and the AOM in the offspring within the age range where we had observations. However, we did find a tendency for the menarcheal age to lower slightly with aging parents (Table II, Model 0). This tendency did not change much for the mothers even after adjusting for age to lower slightly with aging parents (Table II, Model 1). This correlation did not impair the statistical models we have to detect the effects, if any, of advanced age on timing of menarche.

It is possible that parental age has some effect on AOM at higher age levels where we have limited observations. The limited power we have to detect such an effect is not only a result of the rather small number of older people we have but also perhaps the close correlation between maternal and paternal age (R = 0.70, P < 0.0001). This correlation did not impair the statistical models we have used, but it could still be an issue depending on how the biological mechanism operates in determining the timing of menarche in daughters.

The study population had an average AOM of 13.3 years, which is slightly higher than the average age reported for the Copenhagen puberty study population (13.1 years, Akselgaard et al., 2009). A couple of studies have assessed the association between maternal age at birth and timing of menarche in daughters with conflicting results. Rubin et al. had examined the association between AOM and maternal age at delivery as a part of a larger study assessing predictors of early AOM in a cohort who participated in the Avon Longitudinal Study of Parents and Children (ALSPAC). However, the maternal age at delivery was excluded from their final analysis because of insignificant association resulting from their preliminary bivariate analysis (Rubin et al., 1995). Another study, conducted by Cho et al. in a Korean population, examined self-reported AOM in years and maternal age at childbirth adjusted for age and found that younger mothers tended to have daughters with earlier AOM. However, they did not adjust for any other confounders in the analysis and the AOM was collected in years only (Cho et al., 2010).

This study uses longitudinal data that makes clear temporal distinctions between prenatal exposures, perinatal and childhood outcomes. The daughters provided the year and month of menarche, and the follow-up was conducted when the daughters were 17–21 years old. Hence, the self-reported menarcheal age in the late teens or young adulthood is probably more accurate than if reported later in life, or if reported by mothers. However, the recall still covers from 1 to 11 years, thus some recall error is likely as reflected by reporting of both year and month of menarche by only about half of the sample. Furthermore, the majority of the parents were young, reducing the range of parental age at delivery needed to detect the effects, if any, of advanced age on timing of menarche. Only about 9% of mothers and 20% of fathers were 35 years of age or older, the age group many data have indicated as being at high risk for adverse birth and child health outcomes (Fretts et al., 1995; Harlap et al., 2002; Vestergaard et al., 2005; Durkin et al., 2008). The exposure data were collected towards the end of the pregnancy resulting in mostly full-term, normal weight babies and only a very small percentage (<3%) of offspring had low birthweight or pre-term birth. However, these birth outcomes are more likely to be intermediary factors than confounders, given that parental age may be linked to these outcomes.

Advanced maternal age correlates with endocrinological irregularities that may ‘program’ menstrual disorders in their daughters (Smits et al., 1997). Animal studies suggest that advanced parental age may reduce reproductive fitness and fecundity in female offspring (Tarin et al., 2003; Garcia-Palomares et al., 2009). These findings suggest that there may be a moderate association between parental age and timing of menarche as well.

In the past, delayed childbirth was often related to fertility problems. In recent years, with reliable and rather safe contraceptive methods, more fertile individuals are choosing to delay childbearing which has provided us with less biased data to study the potential impact of parental age on their offspring (Gosden and Rutherford, 1995; Heck et al., 1997; Charlton, 2007). Thus, older parents today are expected to have birth and developmental outcomes which differ from those of such parents in the past, which often had fertility or fecundity problems. In this study, although a higher proportion of parents who were 30 years or older reported having undergone fertility treatment (16 versus 5%), they represented less than one-fifth of their own age group. Overall, <9% of mothers reported having ever undergone fertility treatment and about 6% of them reported getting pregnant while using contraceptive methods. Average AOM did not vary much across parents with and without fertility treatment or planned and unplanned pregnancies.

Our finding may be reassuring to many older parents, but a larger study on parents in a higher age range (40 years or older) adjusted for their lifestyle differences is needed to exclude age effects that manifest themselves only above a given age and to differentiate between biological and environmental causes related to delayed parenthood.
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