JOURNAL OF WOMEN'S HEALTH
Volume 20, Number 8, 2011

DOI: 10.1089/jwh.2010.2517

Gestational Weight Gain and Daughter's Age at Menarche

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Abstract

Background: Sexual development begins *in utero* and enters a dormant phase during infancy. The influence of maternal gestational weight gain (GWG) on daughter's age at menarche has not been explored.
Methods: We investigated the association between maternal GWG and age at menarche (<11 years, 11–15 years, >15 years of age) in a large cohort study of U.S. nurses, The Nurses' Health Study II (NHS II), and the Nurses' Mothers' Cohort Study.
Results: Among 32,218 respondents, 7% reported age at menarche <l1, 90% aged 11–15 years, and 3% > age 15. Compared with women whose mothers gained 20–29 lbs during pregnancy, those whose mothers reported <10 lbs or >40 lbs of GWG were 30% more likely to report early onset menarche (<11 years of age) in logistic regression models adjusted for sociodemographic and maternal characteristics, and childhood body size and physical activity: adjusted odds ratio (OR) 1.31, 95% confidence interval (CI) 1.05-1.62, and 1.27, 95% CI 1.06-1.56. Maternal GWG was not associated with late menarche in the fully adjusted model ($p_{trend} = 0.07$).
Conclusions: These results suggest that either extreme of maternal GWG may influence risk for early age at menarche in daughters. Maternal GWG may be a modifiable risk factor for early menarche.

Introduction

Early life exposures may contribute to early onset of puberty[1,2] and age at menarche[3–6] among girls. Sexual development commences *in utero* and extends through early infancy before entering a quiescent phase.[7,8] A number of prenatal exposures have been associated with earlier age at menarche, including organochlorine exposure,[9] maternal cigarette smoking,[10] greater tea intake,[11]and lower physical activity during pregnancy.[12] These early life precursors to puberty may, in part, operate through influences on sex hormone production by the hypothalamic-pituitary-gonadal (HPG) axis. Increasing evidence points to the influence of prenatal and postnatal growth, including birth weight,[13,14] childhood weight gain,[4,15,16] and body composition,[17,18] on age at menarche. Either inadequate or excessive maternal gestational weight gain (GWG) may directly influence perinatal programming of offspring's endocrine functioning through disruption of the fetal hormonal milieu[19,20] and indirectly through prematurity,[21] low or high birth weight,[22] lean body mass,[23] and risk for childhood overweight and obesity.[24]

Maternal GWG has been directly associated with insulin concentrations in infancy, explaining nearly 60% of the variance in these values[25]; cord blood insulin in macrosomic neonates[26]; and neonatal metabolic abnormalities (including hypoglycemia, hypomagnesemia, and hypocalcemia)[27] akin to maternal overweight/obesity.[28] One plausible mechanism linking low birth weight or preterm birth and early age at menarche is insulin resistance and hyperinsulinemia.[29,30] Hyperinsulinism, which is associated with altered adrenal functioning and elevated levels of androgens, has been linked to both restricted prenatal growth and premature pubarche.[30–33]

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Improved understanding of the contribution of intrauterine factors to age at menarche may play a salient role in advancing women's health. Early menarche (<11 years) is associated with risk for metabolic dysfunction, including glucose intolerance, polycystic ovarian syndrome (PCOS), and insulin resistance,[34] breast cancer,[35–37] early sexual activity and teenage pregnancy, depression,[38] and poorer school performance.[39,40] In a retrospective cohort study of mothers who delivered nurse daughters who are members of the Nurses' Health Study, we analyzed the association between maternal GWG and age at menarche using linked maternal-daughter data. We hypothesize that excessive or inadequate maternal GWG may accelerate timing of menarche.

Materials and Methods

Sample

Participants included women in the Nurses' Health Study II (NHS II) whose mothers also participated in the Nurses' Mothers' Cohort Study. The NHS II is an ongoing prospective cohort study started in 1989 with a representative sample of 116,678 registered female nurses born between 1946 and 1965. The Nurses' Mothers' Cohort Study was launched in 2001 with a mail survey to the mothers of NHS I and NHS II participants whose mothers were alive and who did not have a diagnosis of cancer (excluding nonmelanoma skin cancer) ($n=52,166$) in 2000. Details of the prenatal and childhood environment of the

Table 1. Distribution of Nurse's Health Study II Participant Characteristics by Maternal Gestational Weight Gain ($n=32,218$)

	Maternal gestational weight gain (lbs)					
Covariates	*<10*	*10–14*	*15–19*	*20–29*	*30–39*	*≥40*
n (%)	1142 (4)	3,615 (11)	6,776 (21)	13,542 (42)	5,477 (17)	1,666 (5)
Age at menarche, mean (SD)	12.3 (1.5)	12.4 (1.4)	12.5 (1.4)	12.5 (1.4)	12.4 (1.4)	12.4 (1.4)
Participant characteristics						
Age in 1989 in years, mean (SD)	33.9 (4.8)	34 (4.7)	33.7 (4.6)	33.5 (4.6)	33.7 (4.6)	33.9 (4.7)
BMI (kg/m^2) in 1989, mean (SD)	25 (5)	24 (5)	23 (4)	23 (5)	24 (5)	25 (5)
Race/ethnicity, %						
White	94	95	95	95	95	95
Black	0.5	0.5	0.5	0.6	0.5	0.7
Hispanic	2	1	1	1	1	1
Asian	1	1	1	0.5	0.5	0.3
Prenatal factors, mean (SD)						
Birth weight, kg	2.8 (0.6)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)
Gestational age, weeks						
<38	17	15	12	9	8	9
≥38–42	67	68	71	73	72	69
>42	8	6	6	7	9	12
Maternal usual prepregnancy weight, lbs	132 (25)	124 (17)	124 (16)	125 (15)	126 (17)	125 (18)
Maternal height, ft	5.4 (0.2)	5.4 (0.2)	5.4 (0.2)	5.4 (0.2)	5.4 (0.2)	5.4 (0.2)
Paternal height, ft	5.8 (0.2)	5.8 (0.2)	5.9 (0.2)	5.9 (0.2)	5.9 (0.2)	5.9 (0.2)
Maternal age at participant's birth, years	26.4 (5)	26.9 (5)	26.6 (5)	26.3 (5)	25.5 (5)	24 (4.5)
Maternal activity during pregnancy						
Mostly sitting	5	3	3	2	3	5
Mostly standing/walking	18	16	15	17	19	22
Active housework	75	79	80	78	75	71
Heavy manual work	2	3	2	3	3	2
Child household characteristics						
Parental education, %						
≤ High school	48	44	43	45	49	44
College, graduate school	52	56	57	55	50	57
Childhood health behaviors						
Child body size at age 5, %						
Somatogram picture 1	23	24	23	22	21	21
Somatogram picture 2	34	32	34	34	32	31
Somatogram picture 3	23	25	26	26	25	24
Somatogram picture ≥4	19	19	17	19	22	24
Childhood physical activity, %						
Highly active	31	31	30	29	29	31
Active	63	65	66	67	66	63
Mostly inactive/Inactive	5	4	4	4	4	6
Childhood sedentary behaviors, %						
No TV	7	7	7	6	6	4
TV½–2 hours/day	79	80	80	80	77	76
TV >2 hours/day	14	13	13	15	17	20

BMI, body mass index; SD, standard deviation.

nurse participants were reported by the mothers. The response rate of the mothers was 75.6% ($n=39{,}904$), of which 35,794 nurse daughters were members of the NHS II. Information from the mothers' questionnaire was merged with longitudinal data provided by the nurse participants; however, those who were missing data on maternal weight gain during pregnancy ($n=2{,}909$) or age at menarche ($n=107$) or who were members of a twin gestation ($n=560$) were excluded, leaving 32,218 mother-daughter dyads for analysis. The study was approved by the Institutional Review Board at Brigham and Women's Hospital and the National Cancer Institute.

Assessment of exposure and outcome

GWG was reported by the mother from a single item on weight gained during pregnancy, with categorical responses of <10 lbs, 10–14 lbs, 15–19 lbs, 20–29 lbs, 30–40 lbs, >40 lbs, or unknown. In another study population, maternal recall of GWG 30 years after delivery had a Spearman correlation of 0.42 with medical prenatal care and delivery records.[41] Age at menarche was reported by the nurse daughter on the baseline NHS II survey in 1989 from a single question with categorical responses of age ≤9 ($n=535$, 1.7%), 10 ($n=1741$, 5.4%), 11 ($n=5272$, 16.4%), 12 ($n=9809$, 30.5%), 13 ($n=8988$, 27.9%), 14 ($n=3470$, 10.8%), 15 ($n=1372$, 4.3%), 16 ($n=795$, 2.5%), 17+ ($n=236$, 0.7%), or unknown.

We categorized early menarche as those who reported menarche at <11 years and late menarche as those who reported menarche at >15 years and compared each with menarche from ages 11–15 years. As the definitions of early and late menarche are subjective, we used categorizations that have been used in other studies of menarche and breast cancer risk.[42]

Statistical analysis

Multivariable logistic regression models were computed to estimate the odds ratios (OR) after adjustment for factors associated with age at menarche using the SAS PROC LOGISTIC procedure (SAS Institute, 1991). The early menarche analyses contrasted menarche <11 years to menarche 11–15 years, and the late menarche analyses compared menarche >15 years to menarche 11–15 years. Known predictors of age at menarche and strong potential covariates were included in models *a priori* based on biological plausibility, including age of nurse at baseline in 1989 (years) (surrogate for birth cohort), race/ethnicity (Asian, black, Latina, white, other), maternal age at nurse's birth (years), maternal height (feet), paternal height (feet), maternal usual prepregnancy weight (lbs), and socioeconomic status (SES) in childhood based on the highest parental educational attainment at participant's birth (high school graduate or less vs. any advanced education).

We used bivariate regression to explore possible associations of potential confounders with GWG and age at menarche. The following met the criteria for inclusion ($p<0.10$) in our final multivariable model: nurse's birth weight (lbs), gestational age (<38, 38–42, >42 weeks), maternal physical activity during pregnancy (mostly sitting, mostly walking, active housework, heavy manual work), maternal gestational comorbidities (diabetes, hypertension, preeclampsia, urinary tract infection, insulin use during pregnancy; any vs. none), nurse's body shape at age 5 years using somatogram classification scale ranging from 1 to 9 (we grouped the highest categories to create four levels: 1,smallest, 2, 3, ≥4, largest), maternal-reported physical activity (highly active, active, mostly inactive/inactive) of the nurse daughter at age 5 years; and television viewing of the nurse daughter at age 5 years (none, ½–2 hours/day, >2

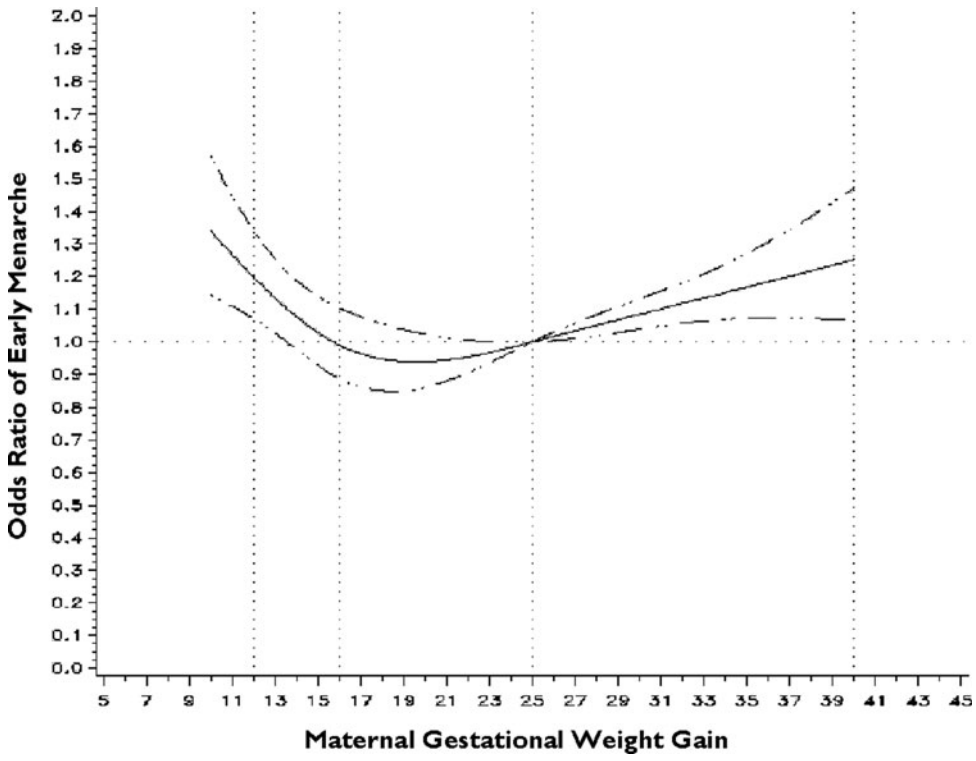

FIG. 1. Cubic spline for maternal gestational weight gain (GWG) predicting risk for early menarche, controlling for age, daughter's race/ethnicity, birth weight, gestational age, maternal prepregnancy weight, maternal height, paternal height, maternal age at daughter's birth, parental education, maternal activity in pregnancy, child body size at age 5 years, childhood physical activity, television viewing. Solid line represents the estimate, and dashed lines represent the 95% confidence interval (CI).

hours/day). The validity of remote recall of childhood body size using somatograms has been found to be reasonably accurate in several studies.[43–46] In one study, the Pearson correlation between remote recall of body size at age 5 and body mass index (BMI) was 0.60.[45] An indicator for missing data was created for each variable to preserve sample size.

We tested nonlinear relations between maternal GWG and early and late menarche using cubic splines.[47] Generalized cross-validation was used to determine the degree of smoothing of spline plots. To assess linearity of the maternal GWG and menarche associations, we compared models with the smoothed maternal GWG term to models with the linear maternal GWG for early and late menarche separately using the likelihood ratio test. For models with evidence of linear associations, a continuous linear term was used in adjusted regression models to examine the trend. For models with evidence of a nonlinear association, categorical indicator variables were used in adjusted regression models. Multivariable logistic regression models were fit using categorical terms for maternal GWG because of the nonlinear association. We conducted likelihood ratio tests comparing models with and without interactions between maternal gestation weight gain and age (< 34 vs. ≥ 34 years) at baseline. The criterion for statistical significance was a 2-sided p value of < 0.05.

Results

Of the 32,218 participants, the majority (90%) reported age at menarche at 11–15 years, while 7% experienced menarche < age 11 ($n = 2{,}317$), and 3% reported onset of menarche > age 15 years ($n = 1{,}048$) (Table 1). Black and Hispanic women were more likely to report early menarche than Caucasian women: 12%, 12%, and 7%, respectively. Lower parental education, maternal physical inactivity in pregnancy, and larger body somatogram at age 5 years were also associated with early menarche. Women whose mothers reported the least GWG (< 10 lbs) tended to weigh less at birth and have mothers of higher prepregnancy weight (Table 1). Women whose mothers reported the highest GWG (> 40 lbs) were more likely to endorse the highest body somatagram at age 5 (24% vs. 19%) and watch > 2 hours/day of television at age 5 (20% vs. 14%) ($p < 0.05$).

Maternal GWG and early menarche

Using cubic spline models for maternal GWG, we observed a nonlinear (U-shaped) association between maternal GWG and risk for early menarche ($p = 0.0032$). A better fit with the cubic spline term was confirmed in comparison of the spline model to a model using the linear term (likelihood ratio test, $p = 0.0059$). As demonstrated by the smoothed plot (Fig. 1), risk for early menarche increases at both extremes of maternal GWG. Notably, maternal GWG of 16–25 lbs was associated with a trend toward lower risk for early menarche (Fig. 1), although this was not statistically significant.

As seen in Table 2, Model 1, women whose mothers had the lowest (< 10 lbs) or highest (> 40 lbs) GWG were more likely to experience menarche before age 11 than those whose mothers gained 20–29 lbs during pregnancy: adjusted ORs were 1.45, 95% CI 1.18-1.79, and 1.32, 95% CI 1.10-1.58, for GWG of < 10 lbs and > 40 lbs, respectively. Women whose mothers gained intermediate amounts of weight, 10–14 lbs, 15–19 lbs,

Table 2. Multivariate Logistic Regression Models of Maternal Gestational Weight Gain and Age at Menarche ($n = 32{,}218$)

		Menarche < 11 years				*Menarche > 15 years*			
	Total n (%)	n (%) *Early menarche*	*Model 1*[a] *Age-adjusted OR (95% CI)*	*Model 2*[b] *Adjusted OR (95% CI)*	*Model 3*[c] *Adjusted OR (95% CI)*	n (%) *Late menarche*	*Model 1*[a] *Age-adjusted OR (95% CI)*	*Model 2*[b] *Adjusted OR (95% CI)*	*Model 3*[c] *Adjusted OR (95% CI)*
Maternal gestational weight gain (lbs)									
< 10	1,153 (4)	108 (9)	1.45 (1.18-1.79)	1.35 (1.09-1.67)	1.31 (1.05-1.62)	41 (4)	1.15 (0.83-1.60)	1.23 (0.86-1.68)	1.21 (0.86-1.67)
10–14	3,654 (11)	278 (8)	1.13 (0.96-1.31)	1.13 (0.98-1.30)	1.08 (0.94-1.25)	120 (3)	1.09 (0.89-1.34)	1.09 (0.88-1.33)	1.08 (0.88-1.33)
15–19	6,829 (21)	449 (7)	0.98 (0.87-1.10)	0.98 (0.87-1.11)	0.97 (0.86-1.10)	244 (4)	1.17 (1.00-1.37)	1.16 (0.99-1.36)	1.16 (0.98-1.36)
20–29	13,729 (42)	913 (7)	1.00 reference	1.00 reference	1.00 reference	424 (3)	1.00 reference	1.00 reference	1.00 reference
30–40	5,645 (17)	413 (7)	1.12 (0.99-1.26)	1.10 (0.98-1.25)	1.10 (0.97-1.25)	169 (3)	0.96 (0.80-1.16)	0.97 (0.81-1.17)	0.98 (0.81-1.17)
> 40	1,768 (5)	156 (9)	1.32 (1.10-1.58)	1.30 (1.08-1.56)	1.27 (1.06-1.54)	50 (3)	0.96 (0.95-0.98)	0.96 (0.71-1.29)	0.98 (0.72-1.33)
			$p = 0.0002$	$p = 0.0015$	$p = 0.0059$		$p_{trend} = 0.04$	$p_{trend} = 0.04$	$p_{trend} = 0.07$

Referent group is average age at menarche (11–15 years old).

[a]Adjusted for age at baseline in 1989 (years).

[b]Adjusted for all covariates in Model 1 and daughter's race/ethnicity(black, white, Hispanic, Asian), birth weight (< 5.5, 5.5–7, 7–8.5, 8.5–10, > 10 lbs), gestational age (< 38, ≥ 38–42, > 42 weeks), maternal prepregnancy weight (lbs), maternal height (ft), paternal height (ft), maternal age at daughter's birth(< 23, 23–26, 27–29, > 29 years), parental education (≤ high school graduate, college or graduate school).

[c]Adjusted for all covariates in Model 2 and maternal activity in pregnancy (mostly sitting, walking, active housework, heavy/manual labor), child body size at age 5 years (somatogram picture 1, 2, 3, ≥ 4), childhood physical activity (highly active, active, mostly inactive/inactive), television viewing (no TV, ½–2, > 2 hours/day).

CI, confidence interval; OR, odds ratio.

or 30–40 lbs, were not at significantly increased risk of early menarche. The observed association between maternal GWG and daughter's age at menarche was modestly attenuated by including sociodemographics, maternal prepregnancy weight, age at daughter's birth, parental height, and birth weight and gestational age (see Model 2) and further attenuated when maternal activity during pregnancy, childhood body size at age 5, physical activity, and television viewing were included in Model 3; ORs were 1.31, 95% CI 1.05-1.62, and 1.27, 95% CI 1.06-1.54, for gestational weight gains of <10 lbs and >40 lbs, respectively.

Maternal GWG and late menarche

We did not find evidence of a nonlinear association between maternal GWG and late onset menarche in models using cubic splines ($p=0.54$). Comparison of models with cubic spline terms and linear terms confirmed a superior fit with the linear term ($p=0.04$). Figure 2 demonstrates the linear association between maternal GWG and risk for late onset menarche.

As demonstrated in Table 2, women whose mothers gained 15–19 lbs during pregnancy were 17% more likely to experience menarche > age 15 compared to women whose mothers reported gestational weight gain of 20–29 lbs in the age-adjusted model. After adjusting for confounders (including maternal age, prepregnancy weight, parental height, education, race/ethnicity, birth weight, gestational age, maternal activity, childhood body size, physical activity, and television viewing), the observed association between maternal GWG and menarche >15 years was no longer statistically significant: adjusted OR 1.16, 95% CI 0.98-1.36 (Table 2). As GWG increased, the odds of late menarche in the daughter decreased (test for trend, $p=0.04$) in the partially adjusted model but was no longer statistically significant ($p=0.07$) in the fully adjusted models.

We repeated all analyses using less stringent criteria, categorizing age at menarche as <12 vs. ≥ 12 years (as 12 years is the median age at menarche in our cohort) and found essentially similar associations (results not shown). We performed sensitivity analyses to evaluate cohort effects by participant's age (assessed as <34 vs. ≥ 34 years) and found no evidence of effect modification between maternal GWG and age at baseline ($p_{\text{interaction}}=0.53$ and 0.44 for models predicting early and late menarche, respectively). Finally, we compared analyses including those with missing covariate data to those with complete data, and results were essentially unchanged.

Discussion

In this study of U.S. nurses and their mothers, we found a U-shaped association between maternal GWG and early menarche in daughters but no significant association with late age at menarche. Risk for early menarche was particularly elevated among daughters exposed to extremes of maternal GWG <10 lbs or $40+$ lbs. This association persisted when controlling for covariates associated with both GWG and age at menarche.

Our findings are consistent with prior studies documenting associations between prenatal characteristics,[1] intrauterine growth parameters, and maternal nutrition and risk for earlier menarche.[14] However, our findings differ from those of Terry et al.[48] who did not find an association between maternal GWG and daughter's age at menarche in a similarly aged cohort of 262 women. The association between maternal GWG and age at menarche may operate through several pathways. First, maternal GWG may be associated with exposure to endocrine factors that influence rate of sexual maturation. Maternal

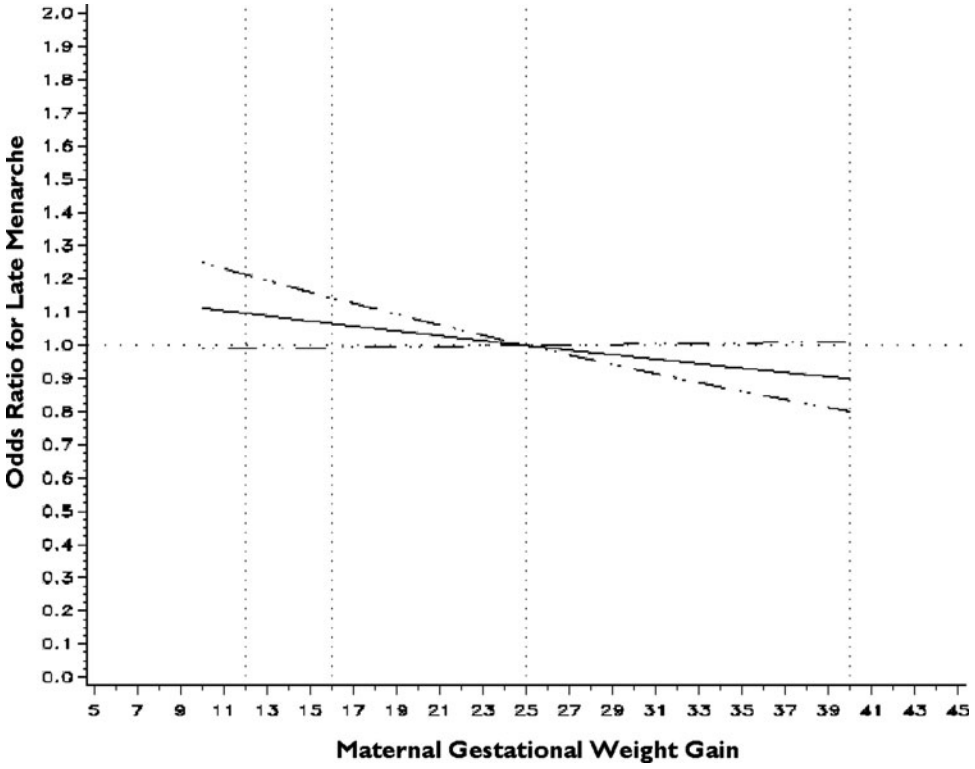

FIG. 2. Linear model for maternal GWG and risk for late menarche, controlling for age, daughter's race/ethnicity, birth weight, gestational age, maternal prepregnancy weight, maternal height, paternal height, maternal age at daughter's birth, parental education, maternal activity in pregnancy, child body size at age 5 years, childhood physical activity, television viewing. Solid line represents the estimate, and dashed lines represent the 95% CI.

plasma leptin level has been associated with GWG,[49] fetal growth,[50] and insulin resistance *in utero*.[28] Second, maternal GWG may influence fetal metabolism and increase risk for insulin resistance, childhood obesity, or rapid weight gain and thereby influence pubertal timing. Relatively higher GWG may reduce insulin sensitivity and causes a hyperglycemic state that may increase placental lactogen, which promotes β-cell replication and thereby elevates risk for fetal hyperinsulinemia.[51] Stuebe et al.[52] have documented an association between extremes of GWG and adolescent and adult obesity in offspring. In our study, birth weight and gestational age appear to attenuate associations between maternal GWG and daughter's age at menarche, suggesting they are on the causal pathway. It is plausible that maternal GWG and daughter's age at menarche may be associated because of shared genetic determinants or lifestyle factors. We adjust for maternal activity, childhood activity, sedentary behaviors, and body size in our analysis of the association between maternal GWG and early menarche. Clearly, biologically plausible mechanisms, which should be investigated in future studies, include epigenetic modifications or fetal metabolic programming *in utero*.

There are several notable limitations. First, age at menarche was reported by the nurses retrospectively. Although studies of the validity of self-reported age at menarche retrospectively are inconsistent,[43,53] we have found that age at menarche is consistently associated with breast cancer risk and is predicted by childhood body size in this cohort.[12,54] Also, whereas maternal prepregnancy weight is accurately recalled, recall of GWG is modestly correlated with data from prenatal records.[41] GWG was reported by the nurse participants' mothers and, therefore, is less likely to be biased than if obtained from the nurse participant, whereas the age at menarche was reported by the nurse daughter 11 years before the maternal study. Moreover, the average age of nurse participants at the time of reporting age at menarche was 34 years, relatively close in timing of menarche; therefore, the likelihood of recall bias is minimized, as has been reported in other well-designed validation studies.[43–45] Moreover, maternal recall of GWG is unlikely to be influenced by daughter's age at menarche, and the resultant nondifferential misclassification is likely to bias results toward the null.

Next, our findings are based on GWG during a period when, relative to today, the standard clinical obstetric practice recommended restriction of weight gain during pregnancy[55]; therefore, it is worthwhile noting the differences in light of current practices. This cohort is predominantly Caucasian nurses, and, therefore, the generalizability of these findings may be limited. Additionally, we use a subset of the larger cohort with maternal information; however, the distribution of age of menarche within the subset and the entire cohort was identical, and this subcohort, therefore, is representative of all NHS II participants with respect to age at menarche. A notable strength of our study is the comprehensive measurement of relevant covariates and the use of reported maternal-child dyad information. Finally, we did not collect data on maternal age at menarche, a recognized factor associated with daughter's age at menarche.[1,6,56]

Conclusions

Our results suggest that maternal GWG is associated with earlier age at menarche in the daughter. There was a modestly significant association between higher maternal GWG and later age at menarche in the daughter. Our findings suggest that the intrauterine environment may be an important factor in timing of menarche. Current trends indicate continued decline in the average age at menarche, with stronger evidence for this association among nonwhites than for Caucasians,[57–60] and declining age of pubertal onset among all U.S. children.[61] At the same time, trends indicate that more women gain excessive weight during pregnancy.[22] Numerous population-level studies have noted an association between earlier age at menarche and breast cancer risk.[62–64] Although the public health implications of early pubertal timing include several significant health consequences, the association with endocrine-related cancers is of particular concern.[65] Pregnancy is a time when women might be more amenable to behavioral change; therefore, our findings build support for the role of intervention during pregnancy or before conception. If replicated, these findings may have implications for the ongoing debate over recommendations about the optimal amount of weight gain during pregnancy. Future research is needed to prospectively explore the association of maternal GWG and age at menarche in a birth cohort study, with repeated measures of biomarker, anthropometric, and clinical indicators of pubertal timing and tempo.

Acknowledgments

We acknowledge the nurse participants in the study and their mothers who participated as well and Dr. Fei Xue for assistance with statistical programming.

This work was supported by William T Grant Foundation, Boston University Building Interdisciplinary Research Careers in Women's Health K12 HD043444 NIH Office of Women's Health Research. The Nurses' Health Study II is supported by Public Health Service grant CA50385 from the National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. The Nurses' Mothers' Cohort Study was funded by the Intramural Research Program of the National Cancer Institute, Research Contract N02-RC-17027 from the National Cancer Institute, and by P.O. 263 MQ 411027 from the National Cancer Institute.

Disclosure Statement

The authors have no conflicts of interest to report.

References

1. Maisonet M, Christensen KY, Rubin C, et al. Role of prenatal characteristics and early growth on pubertal attainment of British girls. Pediatrics 2010;126:e591–e600.
2. Ellis BJ. Timing of pubertal maturation in girls: An integrated life history approach. Psychol Bull 2004;130:920–958.
3. Keim SA, Branum AM, Klebanoff MA, Zemel BS. Maternal body mass index and daughters' age at menarche. Epidemiology 2009;20:677–681.
4. dos Santos Silva I, De Stavola BL, Mann V, Kuh D, Hardy R, Wadsworth ME. Prenatal factors, childhood growth trajectories and age at menarche. Int J Epidemiol 2002;31:405–412.
5. Windham GC, Zhang L, Longnecker MP, Klebanoff M. Maternal smoking, demographic and lifestyle factors in relation to daughter's age at menarche. Paediatr Perinat Epidemiol 2008;22:551–561.

6. Blell M, Pollard TM, Pearce MS. Predictors of age at menarche in the Newcastle Thousand Families Study. J Biosoc Sci 2008;40:563–575.
7. Ebling FJ. The neuroendocrine timing of puberty. Reproduction 2005;129:675–683.
8. Whitlock KE, Illing N, Brideau NJ, Smith KM, Twomey S. Development of GnRH cells: Setting the stage for puberty. Mol Cell Endocrinol 2006;254–255:39–50.
9. Vasiliu O, Muttineni J, Karmaus W. *In utero* exposure to organochlorines and age at menarche. Hum Reprod 2004;19: 1506–1512.
10. Fried PA, James DS, Watkinson B. Growth and pubertal milestones during adolescence in offspring prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2001;23:431–436.
11. Windham GC, Bottomley C, Birner C, Fenster L. Age at menarche in relation to maternal use of tobacco, alcohol, coffee, and tea during pregnancy. Am J Epidemiol 2004;159:862–871.
12. Colbert LH, Graubard BI, Michels KB, Willett WC, Forman MR. Physical activity during pregnancy and age at menarche of the daughter. Cancer Epidemiol Biomarkers Prev 2008;17:2656–2662.
13. Ibanez L, de Zegher F. Puberty and prenatal growth. Mol Cell Endocrinol 2006;254–255:22–25.
14. Adair LS. Size at birth predicts age at menarche. Pediatrics 2001;107:E59.
15. Ibanez L, Ferrer A, Marcos MV, Hierro FR, de Zegher F. Early puberty: Rapid progression and reduced final height in girls with low birth weight. Pediatrics 2000;106:E72.
16. Walvoord EC. The timing of puberty: Is it changing? Does it matter? J Adolesc Health 2010;47:433–439.
17. Sloboda DM, Hart R, Doherty DA, Pennell CE, Hickey M. Age at menarche: Influences of prenatal and postnatal growth. J Clin Endocrinol Metab 2007;92:46–50.
18. Tam CS, de Zegher F, Garnett SP, Baur LA, Cowell CT. Opposing influences of prenatal and postnatal growth on the timing of menarche. J Clin Endocrinol Metab 2006;91: 4369–4373.
19. Holt RI. Fetal programming of the growth hormone-insulin-like growth factor axis. Trends Endocrinol Metab 2002;13: 392–397.
20. Matthews SG. Early programming of the hypothalamo-pituitary-adrenal axis. Trends Endocrinol Metab 2002;13: 373–380.
21. Carmichael S, Abrams B, Selvin S. The association of pattern of maternal weight gain with length of gestation and risk of spontaneous preterm delivery. Paediatr Perinat Epidemiol 1997;11:392–406.
22. Committee on the Impact of Pregnancy Weight on Maternal and Child Health NRC. Influence of pregnancy weight on maternal and child health: Workshop Report (2007). National Academies Press, 2007.
23. Singhal A, Wells J, Cole TJ, Fewtrell M, Lucas A. Programming of lean body mass: A link between birth weight, obesity, and cardiovascular disease? Am J Clin Nutr 2003;77:726–730.
24. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. Am J Obstet Gynecol 2007;196:322 e1–8.
25. Winham DM, Johnston CS, Rhoda KM. Maternal weight gain is associated with infant insulin concentrations during the 1st year of life. Diabetes Care 2006;29:949.
26. Hoegsberg B, Gruppuso PA, Coustan DR. Hyperinsulinemia in macrosomic infants of nondiabetic mothers. Diabetes Care 1993;16:32–36.
27. Crane JM, White J, Murphy P, Burrage L, Hutchens D. The effect of gestational weight gain by body mass index on maternal and neonatal outcomes. J Obstet Gynaecol Can 2009;31:28–35.
28. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. Fetuses of obese mothers develop insulin resistance *in utero*. Diabetes Care 2009;32:1076–1080.
29. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 2003;361:1089–1097.
30. Slyper AH. The pubertal timing controversy in the USA, and a review of possible causative factors for the advance in timing of onset of puberty. Clin Endocrinol (Oxf) 2006;65:1–8.
31. Neville KA, Walker JL. Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity. Arch Dis Child 2005;90:258–261.
32. Ibanez L, Potau N, Francois I, de Zegher F. Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: Relation to reduced fetal growth. J Clin Endocrinol Metab 1998;83:3558–3562.
33. Ibanez L, Potau N, Marcos MV, De Zegher F. Adrenal hyperandrogenism in adolescent girls with a history of low birthweight and precocious pubarche. Clin Endocrinol (Oxf) 2000;53:523–527.
34. Ibanez L, Potau N, de Zegher F. Recognition of a new association: Reduced fetal growth, precocious pubarche, hyperinsulinism and ovarian dysfunction. Ann Endocrinol (Paris) 2000;61:141–142.
35. Petridou E, Syrigou E, Toupadaki N, Zavitsanos X, Willett W, Trichopoulos D. Determinants of age at menarche as early life predictors of breast cancer risk. Int J Cancer 1996; 68:193–198.
36. Romundstad PR, Vatten LJ, Nilsen TI, et al. Birth size in relation to age at menarche and adolescent body size: Implications for breast cancer risk. Int J Cancer 2003;105:400–403.
37. Bernstein L. Epidemiology of endocrine-related risk factors for breast cancer. J Mammary Gland Biol Neoplasia 2002;7: 3–15.
38. Stice E, Presnell K, Bearman SK. Relation of early menarche to depression, eating disorders, substance abuse, and comorbid psychopathology among adolescent girls. Dev Psychol 2001;37:608–619.
39. Johansson T, Ritzen EM. Very long-term follow-up of girls with early and late menarche. Endocr Dev 2005;8:126–136.
40. Graber JA, Seeley JR, Brooks-Gunn J, Lewinsohn PM. Is pubertal timing associated with psychopathology in young adulthood? J Am Acad Child Adolesc Psychiatry 2004;43: 718–726.
41. Tomeo CA, Rich-Edwards JW, Michels KB, et al. Reproducibility and validity of maternal recall of pregnancy-related events. Epidemiology 1999;10:774–777.
42. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: Data from the Nurses' Health Study. Am J Epidemiol 2000;152:950–964.
43. Koprowski C, Coates RJ, Bernstein L. Ability of young women to recall past body size and age at menarche. Obes Res 2001;9:478–485.
44. Must A, Phillips SM, Naumova EN, et al. Recall of early menstrual history and menarcheal body size: After 30 years, how well do women remember? Am J Epidemiol 2002;155: 672–679.
45. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. Am J Epidemiol 1993;138:56–64.

46. Tehard B, van Liere MJ, Com Nougue C, Clavel-Chapelon F. Anthropometric measurements and body silhouette of women: Validity and perception. J Am Diet Assoc 2002;102: 1779–1784.
47. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551–561.
48. Terry MB, Ferris JS, Tehranifar P, Wei Y, Flom JD. Birth weight, postnatal growth, and age at menarche. Am J Epidemiol 2009;170:72–79.
49. Stein TP, Scholl TO, Schluter MD, Schroeder CM. Plasma leptin influences gestational weight gain and postpartum weight retention. Am J Clin Nutr 1998;68:1236–1240.
50. Grisaru-Granovsky S, Samueloff A, Elstein D. The role of leptin in fetal growth: A short review from conception to delivery. Eur J Obstet Gynecol Reprod Biol 2008;136:146–150.
51. Freemark M. Placental hormones and the control of fetal growth. J Clin Endocrinol Metab 2010;95:2054–2057.
52. Stuebe AM, Forman MR, Michels KB. Maternal-recalled gestational weight gain, pre-pregnancy body mass index, and obesity in the daughter. Int J Obes (Lond) 2009;33:743–752.
53. Cooper R, Blell M, Hardy R, et al. Validity of age at menarche self-reported in adulthood. J Epidemiol Community Health 2006;60:993–997.
54. Garland M, Hunter DJ, Colditz GA, et al. Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. Am J Epidemiol 1998;147:636–643.
55. Nutrition during pregnancy. In: Institute of Medicine, Subcommittee on Nutritional Status and Weight Gain during Pregnancy Washington, DC: National Academy Press, 1990.
56. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: Variations around the world, secular trends, and changes after migration. Endocr Rev 2003;24:668–693.
57. Chumlea WC, Schubert CM, Roche AF, et al. Age at menarche and racial comparisons in US girls. Pediatrics 2003;111: 110–113.
58. Demerath EW, Towne B, Chumlea WC, et al. Recent decline in age at menarche: The Fels Longitudinal Study. Am J Hum Biol 2004;16:453–457.
59. Herman-Giddens ME. The decline in the age of menarche in the United States: Should we be concerned? J Adolesc Health 2007;40:201–203.
60. McDowell MA, Brody DJ, Hughes JP. Has age at menarche changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. J Adolesc Health 2007;40:227–331.
61. Biro FM, Galvez MP, Greenspan LC, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. Pediatrics 2010;126:e583–e590.
62. Hsieh CC, Trichopoulos D, Katsouyanni K, Yuasa S. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: Associations and interactions in an international case-control study. Int J Cancer 1990;46:796–800.
63. Okasha M, McCarron P, Gunnell D, Smith GD. Exposures in childhood, adolescence and early adulthood and breast cancer risk: A systematic review of the literature. Breast Cancer Res Treat 2003;78:223–276.
64. Rockhill B, Moorman PG, Newman B. Age at menarche, time to regular cycling, and breast cancer (North Carolina, United States). Cancer Causes Control 1998;9:447–453.
65. Golub MS, Collman GW, Foster PM, et al. Public health implications of altered puberty timing. Pediatrics 2008;121 (Suppl 3):S218–230.

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