



Published in final edited form as:

Matern Child Health J. 2013 October ; 17(8): 1391–1398. doi:10.1007/s10995-012-1139-z.

Maternal Pre-Pregnancy BMI, Gestational Weight Gain, and Age at Menarche in Daughters

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Abstract

Objectives—Life course theory suggests that early life experiences can shape health over a lifetime and across generations. Associations between maternal pregnancy experience and daughters' age at menarche are not well understood. We examined whether maternal pre-pregnancy BMI and gestational weight gain (GWG) were independently related to daughters' age at menarche. Consistent with a life course perspective, we also examined whether maternal GWG, birth weight, and prepubertal BMI mediated the relationship between pre-pregnancy BMI and daughter's menarcheal age.

Methods—We examined 2,497 mother-daughter pairs from the 1979 National Longitudinal Survey of Youth. Survival analysis with Cox proportional hazards was used to estimate whether maternal pre-pregnancy overweight/obesity (BMI 25.0 kg/m²) and GWG adequacy (inadequate, recommended, and excessive) were associated with risk for earlier menarche among girls, controlling for important covariates. Analyses were conducted to examine the mediating roles of GWG adequacy, child birth weight and prepubertal BMI.

Results—Adjusting for covariates, pre-pregnancy overweight/obesity (HR= 1.20, 95% CI 1.06, 1.36) and excess GWG (HR=1.13, 95% CI 1.01, 1.27) were associated with daughters' earlier menarche, while inadequate GWG was not. The association between maternal pre-pregnancy weight and daughters' menarcheal timing was not mediated by daughter's birth weight, prepubertal BMI or maternal GWG.

Conclusions—Maternal factors, before and during pregnancy, are potentially important determinants of daughters' menarcheal timing and are amenable to intervention. Further research is needed to better understand pathways through which these factors operate.

Keywords

Menarche; weight gain; body mass index; pregnancy; cohort studies

Over the past several decades there has been a downward trend in the average age at menarche in the United States and other developed nations (1-4). Girls enter puberty earlier and start menstruating at younger ages than in the past (5). Significant racial disparities exist, with black girls reaching menarche earlier than non-Hispanic white girls (4, 6-9). Life course theory posits that early life experiences influence health over a lifetime and potentially across generations (10-12). Fetal and early childhood programming of

developmental pathways, along with the cumulative effects of certain exposures during key stages of life, can influence health outcomes in adulthood (10, 11, 13). Consistent with a life course perspective, menarche can be seen as a central event in female development, and one that is influenced by early life exposures and subsequently shapes later health outcomes. Early menarche has been associated with heightened risk for a number of deleterious outcomes across the life course, including breast cancer, cardiovascular disease, glucose intolerance and obesity in adulthood, as well as higher rates of depression and risky behaviors during adolescence (14-23).

Studies reveal that a number of hereditary and environmental factors likely influence first menstruation, and that early life factors may be particularly important. Early menarche is correlated with low birth weight, early infant growth patterns, and childhood overweight and obesity (24-29). Factors during pregnancy appear to explain some of these associations. Intrauterine exposures and growth patterns may lead to fetal programming of endocrine, metabolic, and reproductive pathways. Barker's fetal origins hypothesis – also known as the “thrifty phenotype” – postulates that in utero adaptations to certain environmental insults, such as undernutrition, may program the future structure and function of various organs, tissues, and body systems (30). Fetal undernutrition and overnutrition can lead to increased morbidity and mortality later in life (31-33). Few studies, however, have examined whether direct associations exist between maternal factors, including pre-pregnancy BMI and gestational weight gain, and the timing of menarche in offspring.

In 2009, follow-up data from the Collaborative Perinatal Study (1959-1966) found that daughters of obese mothers had an increased risk of early menarche (< 12 years) compared to daughters of normal weight or underweight mothers.(34) In 2011, data from daughters whose mothers participated in the original Nurses' Health Study (1946-1965) showed that maternal gestational weight gain (GWG) was associated with daughters' age at menarche in a U-shaped pattern, such that excessively high (>40lbs) and low (<10lbs) GWG were associated with earlier menarche (35). However, given the homogeneity in that sample (95% non-Hispanic white), it was not possible to assess whether these associations held for other racial/ethnic groups. Moreover, although maternal pre-pregnancy weight was examined as a covariate, it was not included in final models. In 2012, data from daughters whose mothers were in the National Longitudinal Study of Youth 1979 (NLSY79; 1979-1994) were used to estimate the effect of daughters' BMI on their menarcheal timing (36). Results showed that higher prepubertal BMI predicted earlier menarche, and that prepubertal BMI was influenced by mothers' high pre-pregnancy BMI and high gestational weight gain, as well as daughters' birth weight (36). However, this study excluded Hispanic girls and those who had not begun menstruating.

The current study seeks to address these scientific gaps by including Hispanics and using survival analyses, which allows for the inclusion of participants who have not yet menstruated to yield less biased estimates. In addition, consistent with a life course perspective, we examined several mediators of the associations between maternal factors and daughters' menarcheal timing. Specifically, we used NLSY data (1979-2010) to examine the independent effects of maternal pre-pregnancy BMI and GWG adequacy on daughter's age at menarche. We tested whether these associations were consistent across black, non-Hispanic white and Hispanic participants. To our knowledge, this is the first study to include Hispanics and to examine the mediating roles of maternal GWG adequacy, daughter's birth weight, and daughter's prepubertal BMI on the relationship between pre-pregnancy BMI and menarche.

Methods

Participants

The NLSY79 is an ongoing prospective study of a nationally representative sample of 12,686 men and women born between 1957 and 1964 (37). Participants were interviewed annually between 1979 and 1994, and biennially thereafter. Offspring born to women in the original cohort have been surveyed biennially from 1986 to present as part of the NLSY Children and Young Adult survey. Data were completely de-identified and were not subject to human subjects review.

We selected mother-daughter pairs from the larger dataset, and excluded girls with menarche before age 9 (n=34) and after age 16 (n=7) as these events were likely to result from underlying pathology (38). Our sample initially included 3,874 9-16-year old girls assessed from 1988 to 2010. Asian participants were excluded given their low numbers. Data were missing for one or more of the key covariates for 1,377 girls, yielding a final sample that included 2,497 girls with complete data for maternal pre-pregnancy BMI, gestational weight gain, daughters' menarche and covariates. The racial/ethnic breakdown of the final sample was: Black (29.5%), Hispanic (16.1%), and White (54.4%). (For weighted percentages see Table 1.)

Measures

The primary predictor variables were maternal pre-pregnancy BMI and gestational weight gain (GWG) adequacy. Maternal pre-pregnancy BMI (weight [kg]/height [m²]) was calculated based on self-reported pre-pregnancy weight for each gestation and height reported in 1985. Women were categorized as underweight (BMI <18.5), normal weight (BMI <18.5-24.9), and overweight/obese (BMI ≥25.0) (39). There was not sufficient sample size to report overweight and obesity separately, however, sensitivity analyses (not shown) demonstrated that these two categories did not substantially differ.

Optimal GWG is a function of pre-pregnancy BMI as well as length of pregnancy; therefore, we used a previously published algorithm to calculate GWG adequacy (40-42). GWG adequacy was computed as a ratio of the GWG observed for each study woman divided by the expected amount for her pre-pregnancy BMI group and gestational age at delivery multiplied by 100. Observed weight gain was calculated as the difference between self-reported weight at delivery and the pre-pregnancy weight. Expected GWG was defined as 100% of the 2009 IOM recommendations (43) for the mother's gestational age of delivery:

$$\text{Expected gestational weight gain} = \text{recommended first-trimester total weight gain} + (\text{gestational age at weight measurement at or before delivery} - 13 \text{ weeks}) \times \text{recommended rate of gain in second and third trimesters.}$$

We then categorized mother's GWG as inadequate (<88%), adequate (88-123%) or excessive (>123%) based on her percent of the expected IOM weight gain recommendations for gestational age and BMI (41).

The outcome was daughter's age at menarche, which was calculated using date of birth and year and month of first menstruation, reported by mothers for girls under age 14 and self-reported beginning in 1994 for girls age 14 and older. Less than two years of recall were required due to the study design of biennial surveys, and research indicates that retrospective report of age at menarche is reliable, particularly when length of recall is short (44, 45).

Based on the existing literature, we selected the following confounders: socioeconomic status (SES), mothers' race/ethnicity, mother's parity, maternal smoking during pregnancy (yes/no during 12 months before birth of child), maternal age at menarche, and breastfeeding

(yes/no) (2, 34, 35, 46-49). For SES, we included the log parental income (reported at child's birth) and maternal education level (at age 25). Birth weights for daughters born between 22 and 44 weeks gestation were included and were compared to standard U.S. birth weight for gestational age percentile values (50); implausible birth weight-gestational age combinations were excluded (50). Daughters' BMI at age 7 was used to measure prepubertal body composition. BMI at age 6 or 8 was used if weight or height measurements at age 7 were missing. BMI was converted to age- and sex-specific percentiles based on CDC definitions for children (51). Birth weight and prepubertal BMI have well-documented associations with age at menarche (25-27).

Analyses

Analyses were conducted using Stata 12.1. Survey weights were used to account for non-response bias and oversampling of black and Hispanic and low SES populations. We conducted preliminary bivariate analyses using the categorical variable for age of menarche as the outcome. To test for association between this variable and continuous covariates, we used the equivalent of ANOVA for complex sampling designs, implemented in Stata with the survey means command followed by an adjusted Wald test. To test for association between the categorical age of menarche variable and categorical covariates, we used Stata's tabulate command to obtain a P value using the Rao-Scott F approximation to the Pearson chi-square statistic (52).

Survival analysis with Cox-proportional hazards was used to estimate associations adjusting for covariates. First, we examined the association between maternal pre-pregnancy BMI and daughters' age at menarche, adjusting for race/ethnicity, SES, maternal age at menarche, maternal smoking during pregnancy, and whether breastfed. We did not include GWG adequacy in these analyses given the temporal order of the variables (maternal pre-pregnancy BMI precedes GWG). Second, we examined associations between maternal GWG adequacy and daughters' age at menarche, adjusting for all covariates including maternal pre-pregnancy BMI. Third, we examined race/ethnicity by exposure interactions (for pre-pregnancy BMI and GWG adequacy) to determine whether associations with age at menarche held across race/ethnic groups. Last, we examined potential mediators of the association between pre-pregnancy BMI and menarche, including GWG adequacy, birth weight, and daughters' prepubertal BMI.

Survival analysis allowed us to examine time to age at menarche and account for censored data for those girls who had yet to achieve menarche at the time of their last interview. Hazard ratios (HR) can be interpreted similarly to relative risk estimates (52). For categorical exposures, the HR can be interpreted as the instantaneous probability of menarche for girls with as compared to without each exposure, adjusting for covariates. The proportional hazards model assumes that this ratio of probabilities is the same for any age, given that menarche has not yet occurred. For our primary exposures, maternal pre-pregnancy BMI and GWG, "normal pre-pregnancy BMI" and "recommended GWG" served as reference groups in the respective models. We also conducted a sensitivity analysis to analyze high and low GWG (<10lb and >40lb) to compare our findings to those reported from the Nurses Health Studies (35).

Results

Missing data analyses were conducted comparing the excluded mother-child pairs to those included in the final sample. Few significant differences emerged. Those excluded had slightly higher average maternal age at menarche (13.1 vs. 13.0) and slightly higher parity (average of 2.1 vs. 1.8) compared to those who were included. There were no other differences.

Table 1 shows the distribution of variables by four categories of menarche (9-11y, 12y, 13y, 14-16y) for the 2,244 girls with a documented age at menarche and characteristics for the 253 censored girls (who had not attained menarche). Percentages are weighted, except for the final column which presents total raw percentages. Black and Hispanic girls were more likely to experience menarche early (<12 years) compared to white girls. Girls with earlier menarche were more likely to have had lower birth weight, higher prepubertal BMI, and mothers who experienced earlier menarche. About 44% of mothers who were overweight/obese prior to pregnancy had daughters with early menarche compared to those who were normal weight (33.6%) or underweight (27.9%). About 40% of mothers with excessive GWG had daughters with early menarche compared to 35.5% who gained within the recommended range. Pre-pregnancy BMI and gestational weight gain were correlated (not shown): 58.9% of women with a high pre-pregnancy BMI (>25) gained excess gestational weight compared to less than 39.1% of woman with a pre-pregnancy BMI<25.

In the multivariate model examining maternal pre-pregnancy weight and daughters' menarche, we adjusted for all covariates *except* GWG adequacy, given the temporal order of these exposures. Results from the adjusted analysis (Table 2) showed that maternal pre-pregnancy overweight/obesity was associated with earlier menarche (HR=1.20, 95% CI 1.06, 1.36) but underweight pre-pregnancy BMI was not (HR=1.00, 95% CI 0.86, 1.16). In multivariate analyses examining GWG adequacy, we found an association between excessive GWG and age at menarche (HR=1.13, 95% CI 1.02, 1.27), but the association between inadequate GWG and menarche was not significant (HR=1.09, 95% CI 0.96, 1.22). Unadjusted analyses (not shown) suggested that inadequate GWG was associated with earlier menarche; however, this association was no longer significant after adjusting for covariates. To compare our findings to previous research (35), we tested the associations between GWG categories (GWG<10lb and GWG>40lb) and menarche. We found an association for GWG>40lb (HR=1.12, 95% CI 1.00, 1.25) and menarche but not for GWG<10lb (HR=1.19, 95% CI 0.96, 1.47).

Race/ethnicity by exposure interactions (i.e., race by pre-pregnancy weight and race by GWG) were not significant suggesting that associations with age at menarche did not vary across racial/ethnic categories.

Although GWG was associated with pre-pregnancy BMI, it did not appear to mediate the relationship between pre-pregnancy overweight/obesity and age at menarche, as adding GWG to the model did not significantly alter the hazard ratio. Similarly, including daughters' birth weight and prepubertal BMI did not change the hazard ratio, suggesting no evidence for mediation.

Discussion

In this representative sample of women and children, high maternal pre-pregnancy BMI and excessive gestational weight gain (GWG) were associated with daughters' earlier age at menarche. The relationship between pre-pregnancy BMI and menarche, however, was not mediated by maternal GWG adequacy, child birth weight or child prepubertal BMI. Future studies with diverse populations using large samples and well-measured data are needed to further examine the role of these and other mediators. Consistent with prior work, we found that earlier maternal age at menarche, girls' prepubertal BMI, and black race and Hispanic ethnicity were associated with daughters' earlier menarche.

Our findings for pre-pregnancy BMI build upon previous work. Using data from the Collaborative Perinatal Study, Keim et al. reported an association between maternal pre-pregnancy obesity (BMI 30) and early menarche (<12) (OR=3.3, 95% CI=1.1, 10.0) after

adjusting for SES, maternal parity, maternal age at menarche, and daughter's race; however, they did not find increased odds of early menarche for daughters of overweight mothers (OR=1.10, 95% CI = 0.6, 2.1) (34). In our study, we combined overweight and obese mothers and found a significant association with menarche, even when adjusting for these and additional covariates. In addition to combining overweight and obese women in our analyses, our larger sample size may have contributed to our significant findings. Consistent with Keim's results, we found that lower birth weight and higher prepubertal BMI did not significantly mediate the association between maternal pre-pregnancy BMI and daughters' age at menarche.

Mechanisms to explain the relationship between high pre-pregnancy BMI and daughter's early age at menarche are not well understood. One possibility is that fetal size plays a key role, whereby large-for-gestational age (LGA) infants are more likely to become overweight girls, who in turn have an increased risk of earlier menarche. Higher pre-pregnancy BMI has been associated with LGA babies (53); however, our results and Keim's suggest that fetal size does not alter the relationship between high pre-pregnancy BMI and menarche. We also directly tested for mediation of this relationship by GWG, and found no compelling evidence for mediation. In-utero exposures may also be important. For example, since its discovery in 1994, the role of the hormone leptin has also been studied in relation to the onset and progression of puberty (54). Leptin is produced primarily from adipocytes, and concentrations in serum are strongly associated with overall body fat. Serum leptin concentrations have also been shown to increase with girls' pubertal development, presumably through its role in the maturation of the gonadotropin-releasing hormone pulsatile secretions that lead to menses (54, 55). Higher exposures to maternal leptin in-utero – as well as other endocrine hormones, including insulin, insulin-like growth factor I (IGF-I), and growth hormone – could play a role in determining these pathways (24, 56).

Our findings partially support results from the Nurses' Health Studies (35). Consistent with those findings, we found a greater risk for early menarche among girls whose mothers gained >40lb during pregnancy. However, we did not replicate the U-shaped effect; in our sample, low GWG (<10lb) was not significantly associated with earlier menarche. With over 30,000 participants, the Nurses' Health Studies had statistical power to detect differences at both extremes of GWG while our sample was much smaller. Nonetheless, our point estimates were lower than theirs for both GWG>40lb (NHS OR=1.27 vs our HR=1.12) and GWG<10lb (NHS OR=1.31 vs our HR=1.19), suggesting that the lack of association may not simply be due to low power. The examination of GWG extremes in relation to menarcheal timing represents an important area for future investigation, with a particular focus on whether inadequate GWG might play an influential role within certain subpopulations.

Our findings extend those from a recent study, using a subsample of African Americans and non-Hispanic whites from the NLSY, which examined the effect of daughters' prepubertal BMI on menarche and focused on testing racial differences (36). Pre-pregnancy BMI, maternal GWG, and smoking during pregnancy were included as instrumental variables. Results showed that a one standard deviation increase in BMI z-score was associated with a 1.31 month decrease in age at menarche, and that BMI z-score increased with higher birth weight, higher pre-pregnancy BMI, and higher GWG. These findings implied that maternal factors may influence childhood BMI and thereby contribute to menarcheal timing. However, we directly tested this mediational path and did not find prepubertal BMI to act as a mediator. We also examined GWG adequacy and birth weight as potential mediators, but again found no evidence for mediation. Our study was also unique in that we included Hispanic participants and those who had not yet experienced menarche, potentially yielding less biased estimates.

Our study had several potential limitations. The NLSY79 depends on self-reported data, which are subject to error (57). However, age at menarche was reported within 2 years of onset, and self-report of menarche has been found to be reliable up to 30 years later (45). Missing data may limit the generalizability of our results; however, we found few significant and no meaningful differences between participants who were included versus those who were missing data. Another limitation is that we did not have dietary information for mothers or daughters. Diet may play an important role in outcomes associated with weight and weight gain; diet is linked to both weight gain in pregnancy (58, 59) and age at menarche (60-62). It is also reasonable to assume that a daughter's diet is strongly influenced by her mother's dietary patterns.

Our study also had notable strengths. The NLSY is a large, nationally representative prospective study that allowed us to consider many relevant confounders. Our use of survival analysis provided the most appropriate statistical approach given the censored observations. As such, we avoided sample selection bias by including girls who had yet to reach menarche. Given the ethnic diversity of the NLSY, we were able to investigate whether the relationships between the two primary exposures, pre-pregnancy BMI and GWG adequacy, and age at menarche differed by race, and they did not.

Life course theory provides an important conceptual framework for understanding how early life factors may influence health across the life span. Developmental plasticity – or variations in the neurodevelopmental pathway that result from certain environmental events during sensitive periods such as rapid growth – may influence menarcheal timing and subsequently shape downstream health outcomes. As such, research needs to move beyond studying menarche as a single event. The pubertal process, generally, and menarche more specifically, represent critical and potentially vulnerable periods in a woman's life that are intertwined with both early life exposures and later health outcomes. The life course perspective emphasizes that there are multiple opportunities to address maternal and child health at different stages of development -- in infancy, childhood, adolescence, and adulthood (63). Our research suggests that moving even further upstream, to address maternal factors before and during pregnancy, is also critically important.

Ultimately, the health consequences related to early menarche are substantial, and by helping to elucidate pathways to menarcheal age, our findings have important implications for women's health. While timing of girls' menarche is typically not considered to be modifiable, there may be important maternal factors that can be targeted to decrease daughters' risk for early menarcheal timing. High maternal pre-pregnancy weight and gestational weight gain, unlike genetics or maternal age at menarche, may be key targets for clinical and public health interventions (43). Preventive strategies and early interventions to modify these maternal factors, particularly weight before and during pregnancy, have the potential to alter pathways that contribute to early menarche in daughters.

It is particularly important and timely for maternal and child health leaders to advocate for policies and funding that support longitudinal multi-generational studies and intervention research to better understand and intervene on intergenerational effects and developmental markers that have lifelong implications for women's health. Moreover, leaders in the field of maternal and child health are in a unique position to promote a life course perspective when developing programs and policies (63). A commitment to understanding and integrating such a developmental framework into studies of girls' pubertal development is essential to improving maternal and child health nationwide.

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Table 1

Participant characteristics by daughters' age at menarche (n=2,497)

	Girls with documented age at menarche (n=2,244)						Censored (n=253) -- n (%)	Total Weighted %	Total Raw %
	9-11 n (%)	12 n (%)	13 n (%)	14-16 n (%)	p				
Race/ethnicity						0.00	--		
Black (n=718)	548 (48.2)	219 (30.3)	103 (14.5)	48 (7.0)			19 (5.4)	17.4%	
Hispanic (n=378)	171 (44.1)	123 (34.8)	63 (16.0)	21 (5.2)			24 (4.5)	6.8%	
White (n=1,148)	377 (35.8)	414 (35.0)	252 (20.4)	105 (8.9)			210 (90.2)	75.8%	
Maternal pre-pregnancy BMI						0.00			
Underweight (BMI<18.5) (n=187)	59 (27.9)	64 (33.6)	45 (28.2)	19 (10.3)			23 (4.7)	8.2%	
Normal weight (BMI 18.5 & <25.0) (n=1,477)	570 (33.6)	490 (35.4)	288 (20.9)	129 (10.2)			174 (66.9)	66.6%	
Overweight & obese (BMI 25.0) (n=580)	174 (44.3)	141 (34.3)	64 (16.6)	15 (4.9)			36 (28.4)	25.2%	
Maternal GWG						0.01			
Inadequate GWG (n=638)	254 (29.7)	211 (37.3)	129 (21.6)	44 (11.4)			78 (27.9)	25.8%	
Recommended GWG (n=641)	224 (35.5)	211 (35.1)	128 (21.8)	63 (7.7)			71 (28.1)	30.2%	
Excessive GWG (n=965)	418 (40.2)	319 (33.2)	161 (18.9)	67 (7.8)			104 (44.0)	44.0%	
Child birth weight (grams)						0.04	3294.3	--	
3240.9	3295.3	3378.9	3273.2						
Prepubertal BMI						0.00	16.1	--	
16.9	16.3	16.1	15.2						
Maternal age at menarche (yrs)						0.00	13.5	--	
12.7	13.1	13.3	13.8						
Parity						0.05	2.32	--	
1.9	1.9	1.8	1.8						

Note: All percentages and means are weighted except for the Total Raw percentages presented in the final column.

Table 2

Hazard ratios for menarche from survival analysis with Cox proportional hazards

	Hazard ratio	p-value	95% confidence interval
Maternal pre-pregnancy BMI <18.5 (Underweight)*	1.00	0.995	(0.86, 1.16)
Maternal pre-pregnancy BMI >25.0 (Overweight & obese)*	1.20	0.003	(1.06, 1.36)
Excessive gestational weight gain	1.13	0.03	(1.01, 1.27)
Inadequate gestational weight gain	1.09	0.18	(0.96, 1.22)
Maternal age at menarche (months)	0.99	<0.0005	(0.985, 0.991)
Hispanic	1.28	<0.0005	(1.12, 1.46)
Black	1.30	<0.0005	(1.15, 1.47)
Log parental income	1.00	0.91	(0.93, 1.07)
Maternal education (years)	0.98	0.17	(0.96, 1.01)
Maternal smoking during pregnancy	1.12	0.03	(1.01, 1.27)
Daughter breastfed (yes/no)	0.94	0.22	(0.85, 1.04)
Parity	1.00	0.90	(0.95, 1.04)

Note: Adjusted models examining maternal pre-pregnancy BMI and menarche included all covariates listed *except* GWG adequacy given the temporal order of these predictors.