0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(1):46–50
Copyright © 2007 by The Endocrine Society
doi: 10.1210/jc.2006-1378

RAPID COMMUNICATION

Age at Menarche: Influences of Prenatal and Postnatal Growth

Deborah M. Sloboda, Roger Hart, Dorota A. Doherty, Craig E. Pennell, and Martha Hickey

School of Women's and Infants' Health (D.M.S., R.H., D.A.D., C.E.P., M.H.), The University of Western Australia, Perth, Western Australia 6008, Australia; and Women and Infants Research Foundation (D.M.S., D.A.D), Subiaco, Western Australia 6008, Australia

Objective: The objective of this study was to determine the influence of birth weight and postnatal weight gain on age at menarche.

Design, Setting, and Participants: This was a prospective cohort study where girls from the West Australian Pregnancy (Raine) Cohort Study were followed prospectively from fetal life (18 wk of pregnancy) to adolescence (12–14 yr).

Main Outcome Measure: Age at menarche was the main outcome measure.

Results: Growth status at birth was judged by expected birth weight ratio (EBW; a ratio of observed infant's birth weight over median birth weight appropriate for maternal age, weight, height, parity, infant sex, and gestational age). Postnatal growth status was judged by body mass index (BMI). Both EBW ($P = 0.020$) and BMI in childhood (8 yr of age) ($P < 0.001$) were associated with age at menarche. Menarche occurred earlier in girls with lower EBW and higher BMI.

Conclusions: We have demonstrated for the first time that both birth weight and weight gain in childhood are associated with age at menarche. Weight gain before birth and subsequent weight gain up to the age of 8 yr were found to have opposing influences on the timing of menarche. Lower EBW combined with higher BMI during childhood predicted early age at menarche, and this relationship existed across normal birth weight and BMI ranges. **(*J Clin Endocrinol Metab* 92: 46–50, 2007)**

Downloaded from https://academic.oup.com/jcem/article/92/1/46/2597953 by guest on 17 April 2024

IT IS WELL known that many diseases presenting in adolescence and adulthood have early developmental origins. There is increasing evidence suggesting that it is highly likely that reproductive health (menarche, menstrual disorder, polycystic ovarian syndrome) may also be determined by early events (1). Human studies investigating the developmental origins of health and disease have used birth weight as a surrogate marker of developmental influences. The relationship between birth weight and age at menarche has been controversial, and mechanisms regulating this association are unclear. In girls, low birth weight followed by spontaneous catch-up growth has been associated with earlier menarche (2, 3), with reduced ovarian size (4), with reduced ovulation rate (5), and with ovarian hyperandrogenism after precocious pubarche (6). Opposing influences of prenatal and postnatal growth have previously been described for adrenarche (7), central fat distribution (8), and insulin sensitivity at age 8 yr (9).

Menarche, the first menstrual period, occurs between 12–13 yr of age in most developed countries (10) and is the first indicator of reproductive capacity in women. Age at menarche is known to be regulated by factors surrounding the time of puberty, such as adiposity. A minimum body fat mass is required to achieve menarche, and an increased body fat mass is associated with earlier puberty and menarche (11). Childhood obesity is associated with earlier menarche (12) and an increased risk of polycystic ovarian syndrome (13). Compensatory postnatal growth during childhood combined with poor prenatal growth appears to accentuate several adverse health outcomes (14). Knowledge of factors regulating the age of menarche is likely to improve our understanding of female reproductive health. Early menarche is a risk factor for teenage depression (15), insulin resistance (9), and breast cancer in adulthood (16).

The contribution of events during intrauterine and postnatal life on age of menarche in the normal population is poorly understood due to a lack of large prospective cohorts. The Western Australian Pregnancy Cohort (Raine) Study provides unique data to examine the relationship between birth weight and weight gain during childhood to age at menarche.

Subjects and Methods

The Western Australian Pregnancy Cohort (Raine) Study

The Raine Study is an ongoing prospective study originally established to investigate how events during pregnancy and at the time of birth subsequently influence health. This study is one of the largest prospective cohorts of pregnancy, childhood, and now adolescence to be carried out anywhere in the world. In 1989–91, 2900 women were enrolled at 18 wk of pregnancy and their children have been closely followed throughout childhood (http://www.rainestudy.org.au; Fig. 1; Ref. 17).

First Published Online October 24, 2006

Abbreviations: BMI, Body mass index; CI, confidence interval; EBW, expected birth weight ratio; HR, hazard ratio; IQ, interquartile; SGA, small-for-gestational-age.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

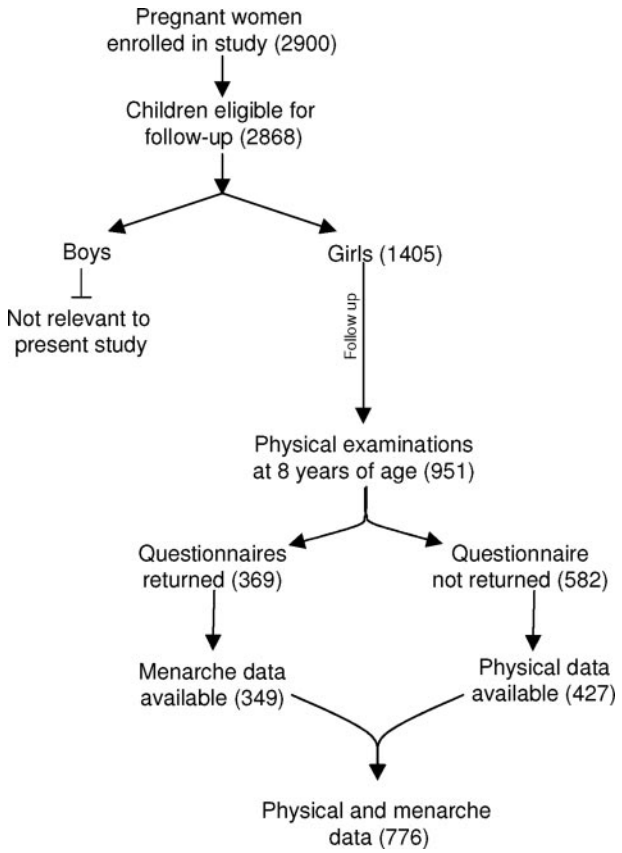

FIG. 1. The West Australian Pregnancy (Raine) Cohort Study participant flow chart is shown. Sample size at each level is depicted in *parentheses*.

Data collected during pregnancy, birth, childhood, and adolescence

Detailed ultrasound fetal growth records were collected during pregnancy as well as extensive maternal clinical data including height, weight, age, and smoking status. Extensive neonatal data were collected including anthropometric measures, weight, length, head circumference, mid-arm, chest, and abdominal circumference; and skin-fold measures (triceps, suprailiac, subscapular, abdominal). This is an ongoing study that includes childhood follow-up (1, 2, 3, 5, 8, 10, and 13 yr of age) when detailed anthropomorphic measures were made (see aforementioned neonatal data). Age at menarche was reported prospectively using a purpose-designed questionnaire (18).

Statistical analyses

Continuous data were summarized using medians, interquartile (IQ) ranges, and ranges. Categorical data were summarized using frequency distributions. Kaplan-Meier survival probabilities were used to estimate the probability of reaching menarche. Multivariable Cox regression analysis was performed to evaluate associations between fetal and postnatal growth and age of menarche. Covariate effects were summarized using hazard ratios (HR) and 95% confidence intervals (CI). Fetal growth was summarized using expected birth weight ratio (EBW; a ratio of observed birth weight over median birth weight appropriate for maternal height, sex, nulliparity, and gestational age). Intrauterine growth restriction was defined as EBW less than 10th percentile. Maternal and pregnancy characteristics and growth data collected up to 8 yr of age were also considered as candidate predictors of age at menarche. Postnatal growth was expressed as body mass index (BMI). Overweight/obesity was defined using BMI and age appropriate cutoffs (19). For those girls who did not return the puberty questionnaire, the age at last follow-up was used for statistical analysis and menarche information was censored. Anthropometric measurements considered as candidate predictors of age at menarche were restricted to those collected up to 8 yr of age because of the requirement that these measurements must precede the earliest age at menarche for all girls in the study. SPSS (SPSS version 11.0; Chicago, IL) statistical software was used for data analyses.

Results

Data are presented on 776 girls from the cohort, of whom 349 had reached menarche. The median age of menarche in these 349 girls was 13.0 yr (IQ range 12.2–14.2; range 9.4–14.6). The median age of girls who had not reached menarche yet was 10.6 yr (IQ range 10.5–13.7; range 10.1–14.3). The median EBW was 1.0 (IQ range 0.93–1.09; range 0.56–1.42). Ninety-one girls (10.5%) were growth restricted at birth as defined previously. EBW predicted age at menarche ($P = 0.020$) and girls with an EBW below the median had a significantly earlier menarche compared with girls with an EBW above the median (HR 1.29, 95% CI 1.04–1.59, $P < 0.001$).

BMI at age 8 yr was independently predictive of age at menarche ($P < 0.001$). BMI at ages 1, 3, and 5 yr was not associated with age at menarche. Median BMI at age 8 was 16.3 (IQ range 15.2–18.0; range 12.2–31.3), and 81 girls (10.4%) were overweight or obese at 8 yr of age. Eight-year-old girls with a BMI above the median had significantly earlier menarche compared with those with BMI below the median (HR 1.65, 95% CI 1.33–2.05, $P < 0.001$). Although no statistically significant interaction between EBW and BMI at 8 yr of age was found ($P = 0.699$), the earliest age at menarche was seen in girls with the lowest EBW and highest BMI (Table 1). Of this group, 71% of girls reached menarche by 13.0 yr (Fig. 2); compared with only 42% of girls who had EBW above the median and BMI (8 yr) below the median. The ranges of age at menarche according to EBW and BMI at 8 yr of age are shown in Table 1.

The following maternal factors were not associated with age at menarche: 1) age, 2) prepregnancy BMI, 3) weight gain during pregnancy, and 4) hypertension and smoking in pregnancy. The following fetal/neonatal factors were not associated with age at menarche: 1) estimated fetal weight (mea-

TABLE 1. Age at menarche: stratified by EBW and BMI at 8 yr of age

EBW and BMI subgroup	Cohort total n	Girls who reached menarche		Median age (yr)	IQ range	Range
		n	% of total			
EBW < 1 and BMI ≥ 16.3	231	120	52	12.5	12.1–13.2	9.4–14.4
EBW ≥ 1 and BMI ≥ 16.3	306	142	46	12.8	12.2–13.6	9.8–14.6
EBW < 1 and BMI < 16.3	127	54	43	13.0	12.6–14.2	10.6–14.6
EBW ≥ 1 and BMI < 16.3	112	33	29	13.2	12.8–14.4	11.0–14.2
Total	776	349				

n, Sample size; EBW and BMI are illustrated as less than (<) or greater than/equal to (≥) the median value for the whole cohort.

Downloaded from https://academic.oup.com/jcem/article/92/1/46/2597953 by guest on 17 April 2024

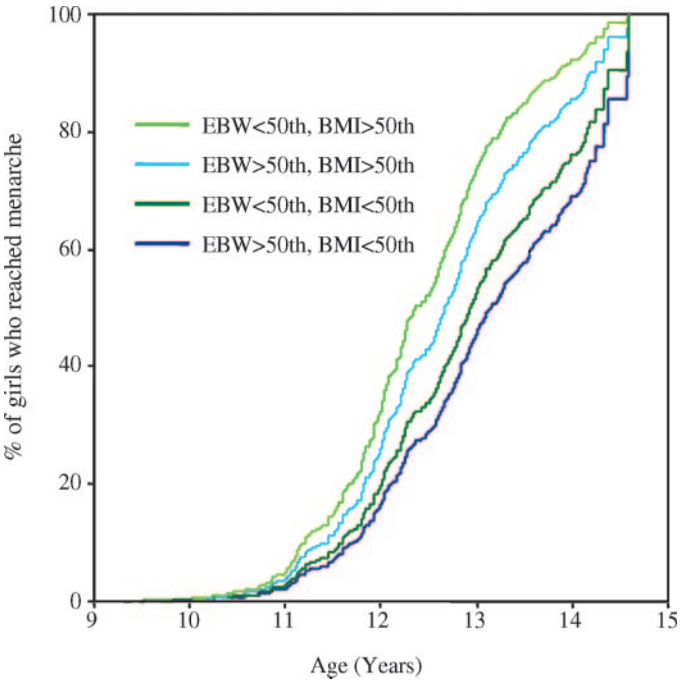

FIG. 2. Kaplan-Meier survival curve demonstrating the relationship between EBW and BMI categorized according to their median values in adolescent girls and age at menarche.

sured by ultrasound) at 18, 24, and 28 wk of pregnancy; 2) head circumference, chest circumference, mid-arm circumference, abdominal circumference, and skin-fold thickness; and 3) height at age 1, 2, 3, and 5 yr. Height at 8 yr of age was associated with age at menarche in the univariate analysis, but was not significant when EBW and BMI at 8 yr of age were also considered.

Discussion

Menarche marks the beginning of reproductive life. It is known to be regulated by childhood events, although mechanisms are poorly understood. Our most significant finding is that both low EBW and high BMI at age 8 yr predicted early age at menarche and that these factors were additive. This combination of low birth weight with accelerated postnatal growth is known to be associated with increased risk of later disease such as diabetes, hypertension, and cardiovascular disease (14). Furthermore, low birth weight and early menarche have been shown to be risk factors for subsequent glucose intolerance in women with polycystic ovarian syndrome (20).

The mechanisms by which intrauterine and childhood growth regulate age at menarche are likely to be multifactorial. The association between BMI and age at menarche has been established previously as a relationship between adiposity and gonadotrophin secretion (21). Low birth weight and rapid weight gain or growth during childhood are independently associated with the occurrence of overweight and obesity later in life (22, 23). Recently, Ibanez *et al.* (24) have shown that between the ages of 2–4 yr, small-for-gestational-age (SGA) children gained more abdominal fat and body adiposity and less lean muscle mass than children born of appropriate size for gestational age. In this study, SGA children developed insulin resistance by the age of 4 yr (24), consistent with previous reports suggesting that regulation of insulin sensitivity is altered in growth-restricted infants (25).

It has been proposed that the mechanism linking weight gain, adiposity, and early pubertal maturation may not be fat/adiposity but hyperinsulinemia and insulin resistance (26). Indeed, the highest incidence of insulin resistance, high plasma total, and low-density lipoprotein cholesterol and fasting insulin levels, were observed in children who had been of low birth weight and at 8 yr of age were of high fat mass and height (9). Ibanez *et al.* (27) have demonstrated that insulin sensitization with metformin decreased circulating leptin and IGF-I levels in low-birth-weight girls and resulted in a delay of menarchal onset by 1 yr. Therefore, it is highly likely that a disruption of the adipo-insular axis regulates the association between early growth restriction, postnatal adiposity, and pubertal development.

In the present study, we have shown that girls with BMI above the median at age 8 demonstrated earlier menarche than those girls with BMI below the median at this age. The earliest age at menarche occurred in girls who were born with an EBW below the median combined with postnatal BMI above the median. Koziel and Jankowska (28) demonstrated that SGA girls who achieved high BMI values at age 14 reached menarche significantly earlier than those girls that were born of average weight for gestational age. Adiposity is regulated by (neuro) endocrine factors such as leptin. As such, the hypothalamic-leptinergic pathway plays a key role in appetite, body fat mass, insulin regulation, and ovarian regulation and may regulate the onset of puberty (1). Leptin levels have been shown to be related inversely to age at menarche, and a gain in body fat of 1 kg lowers the mean time of menarche by 13 d (29). An alteration in leptin regulation is likely to be a contributing mechanism regulating adiposity and age at menarche. Indeed, peripheral leptin resistance is associated with fetal growth restriction and has been suggested to contribute to increases in plasma insulin levels and increased adiposity (30).

Our findings are consistent with those from smaller prospective studies of low-birth-weight girls that have demonstrated associations between low birth weight and exaggerated adrenarche, precocious pubarche, hyperinsulinemia, and ovarian hyperandrogenism and ovulatory dysfunction (5, 31). Our data, together with those previously reported suggest that the association between intrauterine and postnatal growth and age at menarche can be extended to encompass the entire birth weight range, rather than strictly looking at a growth-restricted population. Growth restriction is customarily defined as less than the 10th percentile of weight for gestational age or two SDS below the mean. In the present study, by employing the ratio of the observed to the EBW, growth was considered as a continuous variable allowing greater precision in the analysis of any association of age at menarche with growth. Therefore, known factors associated with birth weight, including maternal age, height, parity, infant sex, and gestation age were accounted for when the association between EBW and age at menarche was determined. One further advantage in our study is that it re-

Downloaded from https://academic.oup.com/jcem/article/92/1/46/2597953 by guest on 17 April 2024

ports on age of menarche in an adolescent cohort from a geographically defined population. The median age at menarche in our cohort is consistent with those previously reported in the literature (10).

This study is not without limitations. Age at menarche was ascertained prospectively from a questionnaire. The possibility that menarchal information was not provided by some girls who reached menarche is a potential source of bias. Our statistical analysis that censored subjects who did not report age at menarche at the time of analysis minimized the effects of underreporting. Furthermore, it is likely that growth trajectories during childhood are also related to reproductive development and the subsequent onset of menarche. At this time, due to sample size limitations, we have assessed childhood growth at specific time points. As a higher proportion of the girls in the cohort reach menarche, growth trajectory analyses spanning antenatal and postnatal periods up to 8 yr of age will become possible.

It is generally accepted that the original observations relating birth size to later risk of disease were not causal but were markers for early life adaptations to developmental events. These adaptations can interact with a dynamic postnatal environment influencing physiology and health. Life history perspectives have been used to interpret the association between poor fetal growth, accelerated childhood weight gain, and age at menarche/puberty (1). It has been proposed that fetal growth restriction, as a consequence of impaired intrauterine conditions, is one component of life history strategy where the organism predicts a shorter life and invests less into growth (1). Early age at menarche (or puberty) may be the interaction of the prenatal influence to advance menarche under poor conditions and the childhood influence to advance menarche under enriched conditions where both events are designed to advance menarche/puberty. This phenomenon has been demonstrated in populations migrating from a poor developing country to a developed country, primarily through international adoption (for review, see Ref. 32). This evidence is consistent with an interaction (and possible conflict) between the prenatal environment and postnatal reality, resulting in significant changes in maturation and, in this case, age at menarche (1).

In conclusion, early age at menarche may be a marker for early life events regulating reproductive, endocrine, and metabolic development that may manifest later in life as polycystic ovarian syndrome, the metabolic syndrome, and potentially breast cancer. Our findings provide further evidence that birth weight (EBW) and childhood overweight may potentially compromise reproductive health in women. Understanding factors determining age at menarche and pinpointing those individuals at risk for these diseases early in life may result in novel interventions or preventative strategies relevant to common diseases of adulthood.

Acknowledgments

We are grateful to The Raine Study Management Team and Executive for their management of the cohort and database. We thank The Raine Study families for their active participation in all aspects pertaining to the ongoing follow-up of their children and The Raine Medical Research Foundation for their support of the cohort.

Received June 27, 2006. Accepted October 16, 2006.

Address all correspondence and requests for reprints to: Dr. D. M. Sloboda, The University of Auckland, Auckland 1142, New Zealand. E-mail: d.sloboda@auckland.ac.nz.

Disclosure Statement: The authors have nothing to disclose.

References

1. **Gluckman PD, Hanson MA** 2006 Evolution, development and timing of puberty. Trends Endocrinol Metab 17:7–12
2. **Ibanez L, Ferrer A, Marcos MV, Hierro FR, de Zegher F** 2000 Early puberty: rapid progression and reduced final height in girls with low birth weight. Pediatrics 106:E72
3. **Ibanez L, de Zegher F** 2006 Puberty after prenatal growth restraint. Horm Res 65(Suppl 3):112–115
4. **Ibanez L, Potau N, Enriquez G, Marcos MV, Zegher FD** 2003 Hypergonadotrophinaemia with reduced uterine and ovarian size in women born small-for-gestational-age. Hum Reprod 18:1565–1569
5. **Ibanez L, Potau N, Ferrer A, Rodriguez-Hierro F, Marcos MV, de Zegher F** 2002 Reduced ovulation rate in adolescent girls born small for gestational age. J Clin Endocrinol Metab 87:3391–3393
6. **Ibanez L, Potau N, Francois I, de Zegher F** 1998 Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: relation to reduced fetal growth. J Clin Endocrinal Metab 83:3558–3562
7. **Ong KK, Potau N, Petry CJ, Jones R, Ness AR, Honour JW, de Zegher F, Ibanez L, Dunger DB** 2004 Opposing influences of prenatal and postnatal weight gain on adrenarche in normal boys and girls. J Clin Endocrinol Metab 89:2647–2651
8. **Garnett SP, Cowell CT, Baur LA, Fay RA, Lee J, Coakley J, Peat JK, Boulton TJ** 2001 Abdominal fat and birth size in healthy prepubertal children. Int J Obes Relat Metab Disord 25:1667–1673
9. **Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V, Bhave S, Kellingray SD, Joglekar C** 1999 Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? Diabetes 48:2422–2429
10. **Whincup PH, Gilg JA, Odoki K, Taylor SJC, Cook DG** 2001 Age of menarche in contemporary British teenagers: survey of girls born between 1982 and 1986. BMJ 322:1095–1096
11. **Blum WF, Englaro P, Hanitsch S, Juul A, Hertel NT, Muller J, Skakkebaek NE, Heiman ML, Birkett M, Attanasio AM, Kiess W, Rascher W** 1997 Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. J Clin Endocrinol Metab 82:2904–2910
12. **Biro FM, Khoury P, Morrison JA** 2006 Influence of obesity on timing of puberty. Int J Androl 29:272–277; discussion 286–90
13. **Laitinen J, Taponen S, Martikainen H, Pouta A, Millwood I, Hartikainen AL, Ruokonen A, Sovio U, McCarthy MI, Franks S, Jarvelin MR** 2003 Body size from birth to adulthood as a predictor of self-reported polycystic ovary syndrome symptoms. Int J Obes Relat Metab Disord 27:710–715
14. **Hales CN, Ozanne SE** 2003 The dangerous road of catch-up growth. J Physiol (Lond) 547:5–10
15. **Kaltiala-Heino R, Kosunen E, Rimpela M** 2003 Pubertal timing, sexual behaviour and self-reported depression in middle adolescence. J Adolesc 26: 531–545
16. **Maskarinec G, Zhang Y, Takata Y, Pagano I, Shumay DM, Goodman MT, Marchand LL, Nomura AM, Wilkens LR, Kolonel LN** 2006 Trends of breast cancer incidence and risk factor prevalence over 25 years. Breast Cancer Res Treat 98:45–55
17. **Newnham JP, Doherty DA, Kendall GE, Zubrick SR, Landau LL, Stanley FJ** 2004 Effects of repeated prenatal ultrasound examinations on childhood outcome up to 8 years of age: follow-up of a randomised controlled trial. Lancet 364:2038–2044
18. **Morris N, Udry R** 1980 Validation of a self-assessment instrument to assess stage of adolescent development. J Youth Adolesc 9:271–278
19. **Cole TJ, Bellizzi MC, Flegal KM, Dietz WH** 2000 Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 320:1240–1245
20. **Gambineri A, Pelusi C, Manicardi E, Vicennati V, Cacciari M, Morselli-Labate AM, Pagotto U, Pasquali R** 2004 Glucose intolerance in a large cohort of mediterranean women with polycystic ovary syndrome: phenotype and associated factors. Diabetes 53:2353–2358
21. **Frisch RE** 1987 Body fat, menarche, fitness and fertility. Hum Reprod 2:521–533
22. **Monteiro POA, Victora CG** 2005 Rapid growth in infancy and childhood and obesity in later life-a systematic review. Obes Rev 6:143–154
23. **Yajnik C** 2000 Interactions of perturbations in intrauterine growth and growth during childhood on the risk of adult-onset disease. Proc Nutr Soc 59:257–265
24. **Ibanez L, Ong K, Dunger DB, de Zegher F** 2006 Early development of adiposity and insulin resistance after catch-up weight gain in small-for-gestational-age children. J Clin Endocrinol Metab 91:2153–2158
25. **Veening MA, van Weissenbruch MM, Delemarre-van de Waal HA** 2002 Glucose tolerance, insulin sensitivity, and insulin secretion in children born small for gestational age. J Clin Endocrinol Metab 87:4657–4661

Downloaded from https://academic.oup.com/jcem/article/92/1/46/2597953 by guest on 17 April 2024

26. **Slyper AH** 2006 The pubertal timing controversy in the USA, and a review of possible causative factors for the advance in timing of onset of puberty. Clinical Endocrinology 65:1–8
27. **Ibanez L, Valls C, Ong K, Dunger DB, de Zegher F** 2006 Metformin therapy during puberty delays menarche, prolongs pubertal growth, and augments adult height: a randomized study in low-birthweight girls with early-normal onset of puberty. J Clin Endocrinol Metab: 91:2068–2073
28. **Koziel S, Jankowska EA** 2002 Effect of low versus normal birthweight on menarche in 14-year-old Polish girls. J Paediatr Child Health 38:268–271
29. **Matkovic V, Ilich JZ, Badenhop NE, Skugor M, Clairmont A, Klisovic D, Landoll JD** 1997 Gain in body fat is inversely related to the nocturnal rise in serum leptin level in young females. J Clin Endocrinol Metab 82:1368–1372
30. **Breier BH, Vickers MH, Ikenasio BA, Chan KY, Wong WP** 2001 Fetal programming of appetite and obesity. Mol Cell Endocrinol 185:73–79
31. **Ibanez L, Jimenez R, de Zegher F** 2006 Early puberty-menarche after precocious pubarche: relation to prenatal growth. Pediatrics 117:117–121
32. **Parent A-S, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon J-P** 2003 The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev 24:668–693

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Downloaded from https://academic.oup.com/jcem/article/92/1/46/2597953 by guest on 17 April 2024