Published in final edited form as:

Fertil Steril. 2011 February ; 95(2): 528–533. doi:10.1016/j.fertnstert.2010.04.057.

Pubertal development of the first cohort of young adults conceived by in-vitro fertilization in the United States

Hind A. Beydoun, PhD^a, Nicholas Sicignano, MPH^a, May Beydoun, PhD^b, Silvina Bocca, MD-PhD^c, Laurel Stadtmauer, MD-PhD^c, and Sergio Oehninger, MD-PhD^{c,*}

^a Graduate Program in Public Health, Eastern Virginia Medical School, Norfolk, VA, USA 23507

^b National Institute on Aging Intramural Research Program, Baltimore, MD, USA 21224

^c Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk, VA, USA 23507

Abstract

Objective—To characterize pubertal development of the first generation of young adults born as a result of in-vitro fertilization (IVF). Demographic, clinical and body size characteristics were examined in relation to developmental milestones.

Design—Cross-sectional.

Setting—Academic center.

Patients—Young adults (18–26 years) conceived by IVF (no gamete/embryo manipulation), 1981–1990.

Intervention—Self-administered questionnaire.

Main outcome measures—Age at puberty onset, body size.

Results—Of 560 eligible young adults, 173 completed the survey (response rate=30.9%). We analyzed data on 166 respondents, 71 males and 95 females. No cases of delayed or precocious puberty were observed in the study sample. As expected, age at puberty onset was significantly higher ($P < 0.0001$) among males (12.3 years) compared to females (11.5 years). A few developmental milestones were predicted by maternal age and infertility diagnoses. For both genders, a direct association was noted between age at puberty onset and height achieved in young adulthood. Structural equations models suggested an inverse relationship of female gender with age at puberty onset and body mass index.

Conclusions—IVF-conceived young adults did not exhibit pubertal abnormalities. Female gender and age at puberty onset independently predicted body mass index of IVF offspring in young adulthood.

Keywords

body mass index; infertility; in-vitro fertilization; puberty

* Address for Correspondence: Sergio Oehninger, MD-PhD, Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, 601 Colley Avenue, 4th floor, Norfolk, VA 23507, Tel: 757-446-7119, Fax: 757 446 5905, OEHNINSC@EVMS.EDU.

Conflict of interest: None.

INTRODUCTION

Assisted reproductive technologies (ART) have been unequivocally shown to be effective methods for overcoming infertility (1). However, ART safety remains a controversial issue and current evidence remains inconclusive as to whether ART can engender adverse short-term and long-term health effects. To date, evaluations of ART safety have mostly been limited to conditions that manifest during the early years of life. While several studies have focused on perinatal outcomes, congenital malformations and epigenetic defects, the few investigations that compared motor, neurological, cognitive and socio-emotional development of ART- and naturally-conceived children have yielded inconsistent results (2–10). A limited number of published studies have followed-up ART-conceived offspring through adolescence; one study went up to 15 years (11) and several others went up to 18 years (12–16) of age.

Pubertal development has rarely been examined in ART populations (17). Variations in puberty onset are thought to be influenced by a mix of genetic and nutritional factors; a historical downward shift in puberty onset has been attributed to the increasing prevalence of childhood obesity (18). Early puberty is thought to be a manifestation of perinatal stress, preterm delivery, low birthweight (LBW) and fetal growth restriction leading to accelerated development, short stature and increased risks of obesity, hyperinsulinemia, type 2 diabetes, cardiovascular disease and reproductive cancers later in life (19–21).

The purpose of this clinical study was to characterize pubertal development in the context of ART. We hypothesized that age of puberty onset can be predicted by maternal age, infertility diagnoses, birth plurality and LBW, which are typical of ART populations. We further hypothesized that the effects of maternal age, infertility diagnoses, LBW and birth plurality on body size of ART-conceived young adults is partly mediated by age at puberty onset. Our analyses are based on a cross-sectional evaluation of the first U.S. cohort of young adults conceived between 1981 and 1990 by in-vitro fertilization (IVF) at our center (22). Our program reported the first IVF birth in the U.S. (Elizabeth Carr), who was also the first successful pregnancy achieved using gonadotropin stimulation (23).

METHODS

The Institutional Review Board approved the study with a waiver of informed consent. Young adults, 18–26 years of age, conceived by IVF were recruited and enrolled into the study through their parents. At the time, neither oocyte nor embryo micromanipulation were applied; however, a limited number of infants were conceived through gamete donation or frozen embryos. Diagnostic, treatment and outcomes data are routinely stored in a specialized database for patients seeking treatment. A list of IVF cycles that resulted in a live birth was created and a sampling frame was generated by reconciling this list against a mailing list. A contact list was created by applying a set of eligibility criteria to the sampling frame. Former patients were included on the contact list if they sought IVF treatment between January 1st, 1981 and December 31st, 1990 and delivered at least one liveborn infant. There were 840 IVF-conceived live births; those who had previously indicated their unwillingness to ever be contacted (10 singleton deliveries), 25 deceased babies (10 singletons, 14 babies from 7 twin pregnancies, and 1 baby from a triplet pregnancy), and 245 young adults that could not be contacted for various reasons (mainly inability to be located, inaccessible parents addresses), were excluded. As such, 560 young adults delivered to 417 former patients met all eligibility criteria.

An initial letter and two follow-up letters were mass-mailed to former patients on the contact list, i.e. the parents of the IVF-conceived young adults. At the closing date of the survey,

209 (50.1%) of the former patients had not replied to initial or follow-up letters, 18 (4.3%) were deemed untraceable and 17 (4.1%) refused to participate, leaving 173 parents (41.4%) who had forwarded survey materials to their eligible young adults; 173 of 189 (91.5%) young adults who were provided access to survey materials completed the survey by the closing date. Of 146 mothers to the 173 respondents, 9 (6.2%) conceived through egg donation and 3 (2.0%) conceived through sperm donation; 7 of the 173 respondents were outcomes of frozen embryos. The estimated response rate was 31%. Whereas respondents (n=173) and non-respondents (n=387) did not differ significantly in terms of age or birth plurality, the proportion of females was considerably higher among respondents compared to non-respondents (56.6% versus 42.6%; $P=0.002$). The vast majority of respondents were non-Hispanic whites born in the U.S, and this was not different from non-respondents. Current analyses for the present study were restricted to 166 respondents (71 males and 95 females) whose survey could be linked to diagnostic, treatment and outcomes data from the available IVF database.

The survey instrument was entirely focused on assessing young adults and no parental data were obtained. A 90-item self-administered questionnaire was used to collect data on demographics, employment, health status, physical development, self-perceptions, anxiety and depression, health behaviors and chronic diseases. Questions assessing pubertal development (growth spurt, body hair, skin changes, voice changes, facial hair, breast development and menarche) were adapted from the Project on Human Development in Chicago Neighborhoods (PHDCN) Longitudinal Cohort Study. In the original PHDCN questionnaire, survey respondents were asked to self-report their current stage with regard to each of these developmental milestones. Possible responses for these questions were 'no change', 'barely started', 'definitely underway' and 'completed'. In our survey, age at onset of each developmental milestone was also evaluated among respondents who reported a physical change as a result of puberty. In addition, respondents were asked to directly report their age at puberty onset ('Approximately, at what age did you start noticing changes related to puberty?') Demographic (gender, age) and clinical (maternal age, infertility diagnosis, birth plurality, LBW) characteristics were assessed in relation to developmental milestones. Young adults' gender and age were self-reported, while maternal age and infertility diagnoses were obtained from the IVF database. Birth plurality was assessed by asking respondents 'Were you an outcome of a single, twin, triplet, quadruplet or more pregnancy?' and was recoded as 'singleton' or 'multiple'. LBW status was based on self-report and was defined as '< 2500 grams' or ' ≤ 2500 grams'. Indicators of body size, namely weight, height and BMI, were obtained through self-report. BMI (kg/m^2) was calculated as weight (kg) divided by height squared (m^2).

Statistical analyses were conducted using SAS version 9.1. Two-sided statistical tests were performed at a α level of 0.05. First, demographic, clinical, anthropometric and developmental characteristics were described. Second, ordinary least squares (OLS) models were constructed to examine each demographic or clinical characteristic as a predictor of selected developmental milestones. OLS models were also constructed to examine developmental milestones as predictors of weight, height and BMI. Using SAS CALIS procedure, structural equations models (SM) were created to estimate the direct, indirect and total effects of demographic and clinical characteristics on weight, height and BMI, respectively, through age at puberty onset.

RESULTS

Table 1 displays basic characteristics of the 166 young adult respondents. On average, mothers of respondents were 34 years (range: 27–42) of age at IVF initiation. Primary diagnoses associated with IVF treatment were tubal (57%), endometriosis (16%) and male

factor (15%) infertility. The mean age of respondents was 21.2 years; 38% were outcomes of multiple gestations (51 twins, 7 triplets and 4 quadruplets) and 12% were LBW. At the time of survey completion, mean ($\pm$ standard error) weight, height and BMI of young adults were 75.1 ($\pm$ 1.3) kilograms, 1.7 ($\pm$ 0.008) meters and 25.3 ($\pm$ 0.3) kg/m², respectively. These anthropometric measures nearly coincide with the mean ($\pm$ standard error) weight (76.95 $\pm$ 1.19 kilograms), height (1.7 $\pm$ 0.004 meters) and BMI (25.9 $\pm$ 0.4 kg/m²) of non-Hispanic whites 18–26 years of age from the 2005–2008 National Health and Nutrition Examination Study (NHANES) (data not shown).

As shown in Table 2, no cases of delayed or precocious puberty were observed in the study sample. The latest age at onset of a developmental milestone was 19 years. All males reported an onset of puberty at 10 years of age or later. Two females reported an onset of puberty at 8 years and another seven females at 9 years of age. Early menarche was reported by four females whose first menstrual period started at 10 years of age. Mean age at puberty onset was approximately 12 years and was significantly higher among males compared to females (12.3 years versus 11.7 years, $P < 0.0001$).

Table 3 presents associations between demographic and clinical characteristics and gender-specific developmental milestones. Birth plurality and LBW had no significant effects on age at onset of growth spurt, body hair, skin changes, voice changes, facial hair, breast development or menarche. Among males, age at puberty onset was directly and significantly associated with tubal infertility ($\beta = 0.6$; $P = 0.04$). Among females, maternal age was inversely related to age at breast development ($\beta = -0.1$; $P = 0.05$), endometriosis was inversely related to age at menarche ($\beta = -1.2$; $P = 0.009$) and a direct association was noted for rare diagnoses involving the cervix, the immune system or exposure to diethylstilbestrol in relation to age at onset of growth spurt ($\beta = 1.5$; $P = 0.003$).

Table 4 presents pubertal onset milestones as predictors of weight, height and BMI before and after stratifying by gender. Height attained by young adults was directly related to ages at onset of puberty, growth spurt, body hair and skin changes. Furthermore, age at onset of growth spurt was inversely related to weight among males and to BMI among males and females. Age at onset of voice changes and facial hair among males were inversely related to weight, whereas age at onset of facial hair was inversely associated with BMI. Finally, age at menarche was inversely associated with BMI among females.

SM were constructed for gender, age, maternal age, infertility diagnosis, age at puberty onset and indicators of body size, namely weight, height and BMI. Results suggested that female gender was the only factor showing statistical significance and was inversely related to age at puberty onset, weight and height, after adjustment for other variables in the SM. By contrast, female gender and age at puberty onset were both significantly and inversely related to BMI.

DISCUSSION

In this study, we evaluated variations in age at puberty onset and related developmental milestones according to selected demographic and clinical characteristics of young adults conceived by IVF. We further evaluated whether these developmental milestones might affect body size in young adulthood. As expected, puberty was initiated at approximately 12 years of age, with females maturing one year earlier than males. Body size indicators were also within the expected range of non-Hispanic white U.S. young adults, 18–26 years of age. No cases of delayed or precocious puberty were observed in our study sample. While birth plurality and LBW had no effect on puberty onset, maternal age and specific infertility diagnoses were associated with certain aspects of pubertal development. A direct

relationship was noted between age at puberty onset and adult height, irrespective of gender. SM indicated that the relationship between female gender and BMI in young adulthood was partly mediated by age at puberty onset.

Although the future fertility of children conceived by IVF is a major concern for their parents (24), the recent nature of these procedures has so far, precluded the conduct of large studies that focus on pubertal development and pregnancy potential. Rojas-Marcos (17) described a case-series of 7 ART-conceived infants (5–21 months of age) who presented with breast development or pubic hair. Endocrine evaluation and pelvic sonography confirmed pre-pubertal status; however, clinical follow-up did not reveal progression of breast development, pubarche or elevation in sex steroids (17).

Neville (19) conducted a retrospective chart review of 89 children diagnosed with precocious pubarche and concluded that both prematurity and small-for-gestational age were associated with precocious pubarche. Perinatal stress is expected to be more prevalent in IVF-conceived than in naturally conceived live births, rendering them at higher risk for precocious pubarche, a rare but potentially detrimental condition whereby pubic hair appears prior to 8 years of age among females or prior to 9 years of age among males (19). None of our respondents reported early pubarche; in fact, body hair appeared between 10 and 16 years of age for males and females in our sample.

The link between prenatal exposures, pubertal development and body size is consistent with the Barker hypothesis (25). As a result of stress, fetuses often adapt to a limited supply of nutrients and consequently their physiology and metabolism are permanently altered. This fetal programming is thought to be the origin of obesity-related health problems including coronary heart disease, stroke, diabetes and hypertension (25). In a recent study, Rubin (26) used survival models to analyze factors related to timing of puberty among 8 to 13-year old girls enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC); factors that predicted early menarche (prior to 11 years of age) were earlier maternal age at menarche, high maternal pre-pregnancy BMI, smoking during the third trimester, non-white race and body size at 8 years of age (26). While these findings imply a simultaneous role of genetic and environmental factors, they also suggest that body size at early stages of development can predict pubertal development. Thus, the observed inverse relationship between puberty onset and BMI in young adulthood may be an artifact since a high BMI in childhood contributes to early maturation and is often correlated with a high BMI at later stages of life. Similarly, prenatal stress may predispose to earlier maturation through fetal programming which also leads to short stature in young adulthood.

The present results need to be interpreted cautiously in light of several limitations. First, the cross-sectional design can preclude ascertainment of temporal relationships. Second, due to its geographically dispersed nature, no adequate comparison group could be identified for this first cohort of IVF young adults. Third, low response rate and retrospective self-reporting can result in self-selection and measurement bias, respectively. Survey non-respondents may have included young adults with developmental abnormalities that affected their ability to partake in the study. In addition, questions that were used to assess pubertal development, which were adapted from a longitudinal study, have not been validated for this population. With the exception of menarche, subjects may experience difficulties in the retrospective recall of developmental milestones, leading to misreporting or rounding based on common knowledge about typical development.

In conclusion, our study found no cases of pubertal abnormalities among IVF-conceived offspring that responded to the survey. Female gender and age at puberty onset independently predicted body mass index of IVF offspring in young adulthood.

Acknowledgments

No funding was provided for this project. However, this research was supported in part by the intramural research program of the NIH, National Institute on Aging. We are indebted to Helena Russell, MS, Mrs. Nancy Garcia and Ms. Debi Jones for assistance with computerized database, mailings and collection of information. We are very thankful to Dr. Howard Jones for helpful discussions and suggestions.

References

1. Cederblad M, Friberg B, Ploman F, Sjoberg NO, Stjernqvist K, Zackrisson E. Intelligence and behaviour in children born after in-vitro fertilization treatment. *Hum Reprod* 1996;11:2052–7. [PubMed: 8921089]
2. Wang J, Sauer MV. In vitro fertilization (IVF): a review of 3 decades of clinical innovation and technological advancement. *Ther Clin Risk Manag* 2006;2:355–64. [PubMed: 18360648]
3. Propping P. Assisted reproduction: an important review of the literature on the risk of malformation after in vitro fertilization and intracytoplasmic sperm injection. *Deutsches Arzteblatt international* 2008;105:9–10. [PubMed: 19578447]
4. Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Van Geijn HP. Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. *J Psychosom Res* 1995;39:563–95. [PubMed: 7490693]
5. McDonald SD, Murphy K, Beyene J, Ohlsson A. Perinatal outcomes of singleton pregnancies achieved by in vitro fertilization: a systematic review and meta-analysis. *J Obstet Gynaecol Can* 2005;27:449–59. [PubMed: 16100639]
6. McDonald SD, Han Z, Mulla S, et al. Preterm birth and low birth weight among in vitro fertilization twins: a systematic review and meta-analyses. *Eur J Obstet Gynecol Reprod Biol* 2010;148:105–13. [PubMed: 19833428]
7. McDonald S, Murphy K, Beyene J, Ohlsson A. Perinatal outcomes of in vitro fertilization twins: a systematic review and meta-analyses. *Am J Obstet Gynecol* 2005;193:141–52. [PubMed: 16021072]
8. Ludwig AK, Sutcliffe AG, Diedrich K, Ludwig M. Post-neonatal health and development of children born after assisted reproduction: a systematic review of controlled studies. *Eur J Obstet Gynecol Reprod Biol* 2006;127:3–25. [PubMed: 16621225]
9. Hvidtjorn D, Schieve L, Schendel D, Jacobsson B, Svaerke C, Thorsen P. Cerebral palsy, autism spectrum disorders, and developmental delay in children born after assisted conception: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med* 2009;163:72–83. [PubMed: 19124707]
10. Brewaeys A. Review: parent-child relationships and child development in donor insemination families. *Hum Reprod Update* 2001;7:38–46. [PubMed: 11212073]
11. Bruinsma F, Venn A, Lancaster P, Speirs A, Healy D. Incidence of cancer in children born after in-vitro fertilization. *Hum Reprod* 2000;15:604–7. [PubMed: 10686204]
12. Ceelen M, van Weissenbruch MM, Roos JC, Vermeiden JP, van Leeuwen FE, Delemarre-van de Waal HA. Body composition in children and adolescents born after in vitro fertilization or spontaneous conception. *J Clin Endocrinol Metab* 2007;92:3417–23. [PubMed: 17595253]
13. Ceelen M, van Weissenbruch MM, Vermeiden JP, van Leeuwen FE, Delemarre-van de Waal HA. Cardiometabolic differences in children born after in vitro fertilization: follow-up study. *J Clin Endocrinol Metab* 2008;93:1682–8. [PubMed: 18285409]
14. Wagenaar K, Ceelen M, van Weissenbruch MM, Knol DL, Delemarre-van de Waal HA, Huisman J. School functioning in 8- to 18-year-old children born after in vitro fertilization. *Eur J Pediatr* 2008;167:1289–95. [PubMed: 18270734]
15. Wagenaar K, van Weissenbruch MM, Knol DL, Cohen-Kettenis PT, Delemarre-van de Waal HA, Huisman J. Behavior and socioemotional functioning in 9–18-year-old children born after in vitro fertilization. *Fertility Steril* 2009;92:1907–14.
16. Ceelen M, van Weissenbruch MM, Prein J, Smit JJ, Vermeiden JP, Spreeuwenberg M, et al. Growth during infancy and early childhood in relation to blood pressure and body fat measures at

- age 8–18 years of IVF children and spontaneously conceived controls born to subfertile parents. *Hum Reprod* 2009;24:2788–95. [PubMed: 19648588]
17. Rojas-Marcos PM, David R, Kohn B. Hormonal effects in infants conceived by assisted reproductive technology. *Pediatrics* 2005;116:190–4. [PubMed: 15995052]
 18. 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. *Clinical endocrinology* 2006;65:1–8. [PubMed: 16817811]
 19. Neville KA, Walker JL. Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity. *Archives of disease in childhood* 2005;90:258–61. [PubMed: 15723910]
 20. Golub MS, Collman GW, Foster PM, Kimmel CA, Rajpert-De Meyts E, Reiter EO, et al. Public health implications of altered puberty timing. *Pediatrics* 2008;121 (Suppl 3):S218–30. [PubMed: 18245514]
 21. Ten S, Maclaren N. Insulin resistance syndrome in children. *J Clin Endocrinol Metab* 2004;89:2526–39. [PubMed: 15181020]
 22. Beydoun HA, Sicignano N, Beydoun MA, Matson DO, Bocca S, Stadtmauer L, et al. A cross-sectional evaluation of the first cohort of young adults conceived by in vitro fertilization in the United States. *Fertil Steril*. 2010 In press. 10.1016/j.fertnstert.2009.12.023
 23. Jones HW Jr, Jones GS, Andrews MC, Acosta A, Bundren C, Garcia J, et al. The program for in vitro fertilization at Norfolk. *Fertil Steril* 1982;38:14–21. [PubMed: 7095165]
 24. Fisher-Jeffes LJ, Banerjee I, Sutcliffe AG. Parents' concerns regarding their ART children. *Reproduction* 2006;131:389–94. [PubMed: 16452732]
 25. Barker DJ. The intrauterine origins of cardiovascular and obstructive lung disease in adult life. The Marc Daniels Lecture 1990. *J R Coll Physicians Lond* 1991;25:129–33. [PubMed: 2066923]
 26. Rubin C, Maisonet M, Kieszak S, Monteilh C, Holmes A, Flanders D, et al. Timing of maturation and predictors of menarche in girls enrolled in a contemporary British cohort. *Paediatr Perinat Epidemiol* 2009;23:492–504. [PubMed: 19689500]

Table 1

Characteristics of survey respondents (n=166)

Characteristic	N	Value
Male gender, %	166	42.8
Female gender, %	166	57.2
Multiple gestation, %	165	37.6
Low birthweight, %	143	11.9
Infertility diagnosis, %		
Anovulation	162	3.7
Cervical/diethylstilbestrol/immunological	162	3.1
Endometriosis	162	16.1
Idiopathic	162	4.9
Male factor	162	15.4
Tubal	162	56.8
Age of respondent, years: median, mean (SD)	166	21.0, 21.2 (2.2)
Maternal age at delivery, years: median, mean (SD)	166	34.0, 34.1 (3.3)
Weight, kg: median, mean (SD)	159	72.5, 75.1 (16.2)
Height, m: median, mean (SD)	166	1.7, 1.7 (0.1)
BMI, kg/m ² : median, mean (SD)	159	24.8, 25.3 (3.7)

BMI=body mass index; SD=standard deviation.

Table 2

Age at onset of pubertal milestones by gender in survey respondents (N=166)

	Total			Gender			P value
	n	Mean (SD) Range	n	Mean (SD) Range	n	Mean (SD) Range	
<i>Age at onset:</i>							
Puberty	164	12.1 (1.6) 8–16	71	12.6 (1.3) 10–16	93	11.7 (1.7) 8–16	< 0.0001
Growth	158	12.4 (1.8) 10–18	70	13.2 (1.8) 10–18	88	11.7 (1.6) 10–16	< 0.0001
Body hair	161	12.3 (1.6) 10–16	70	12.7 (1.4) 10–16	91	12.0 (1.6) 10–16	0.003
Skin changes	147	13.3 (1.8) 10–19	65	13.8 (1.5) 11–18	82	12.9 (2.0) 10–19	0.007
Voice changes ^a	69	13.9 (1.6) 11–17	69	13.9 (1.6) 11–17	--	--	--
Facial hair ^a	71	15.2 (1.9) 10–19	71	15.2 (1.9) 10–19	--	--	--
Breasts ^b	94	12.2 (1.7) 10–17	--	--	94	12.2 (1.7) 10–17	--
Menarche ^b	91	12.6 (1.5) 10–17	--	--	91	12.6 (1.5) 10–17	--

SD=standard deviation;

^aQuestion addressed to males only;^bQuestion addressed to females only.

Table 3

Association of demographic and clinical characteristics with age at onset of pubertal milestones stratified by gender

Age at onset of pubertal milestones – Males										Age at onset of pubertal milestones – Females									
Demographic and clinical characteristics			Puberty		Growth		Body hair		Skin changes		Voice changes		Facial hair						
			β	SEM	β	SEM	β	SEM	β	SEM	β	SEM	β	SEM					
Age	0.04 ^{ns}	0.07	-0.1 ^{ns}	0.09	-0.01 ^{ns}	0.07	-0.09 ^{ns}	0.08	-0.15 ^{ns}	0.08	-0.03 ^{ns}	0.1	0.06						
Maternal age	-0.07 ^{ns}	0.04	-0.02 ^{ns}	0.06	-0.06 ^{ns}	0.05	-0.06 ^{ns}	0.05	-0.07 ^{ns}	0.05	-0.09 ^{ns}	0.06	0.06						
Multiple gestation	0.02 ^{ns}	0.3	0.1 ^{ns}	0.4	0.1 ^{ns}	0.4	-0.3 ^{ns}	0.4	0.2 ^{ns}	0.4	0.8 ^{ns}	0.5	0.5						
Low birthweight	-0.7 ^{ns}	0.6	0.5 ^{ns}	0.8	0.4 ^{ns}	0.6	0.08 ^{ns}	0.7	-0.06 ^{ns}	0.8	-0.2 ^{ns}	0.9	0.9						
Anovulation	0.3 ^{ns}	1.3	-0.2 ^{ns}	1.8	0.2 ^{ns}	1.5	0.2 ^{ns}	1.5	1.1 ^{ns}	1.6	0.8 ^{ns}	1.9	1.9						
Cervical/diethylstilbestrol/immunological	--	--	--	--	--	--	--	--	--	--	--	--	--						
Endometriosis	-0.2 ^{ns}	0.4	0.1 ^{ns}	0.6	-0.1 ^{ns}	0.5	0.04 ^{ns}	0.5	0.7 ^{ns}	0.5	0.2 ^{ns}	0.6	0.6						
Idiopathic	-0.009 ^{ns}	0.8	-0.6 ^{ns}	1.1	-0.4 ^{ns}	0.9	-0.3 ^{ns}	0.8	-0.6 ^{ns}	0.9	-1.3 ^{ns}	1.1	1.1						
Male	-0.6 ^{ns}	0.4	-0.4 ^{ns}	0.6	-0.4 ^{ns}	0.5	0.04 ^{ns}	0.5	-0.1 ^{ns}	0.5	-0.3 ^{ns}	0.6	0.6						
Tubal	0.6 ^a	0.3	0.3 ^{ns}	0.4	0.5 ^{ns}	0.3	0.03 ^{ns}	0.4	-0.2 ^{ns}	0.4	0.3 ^{ns}	0.4	0.4						

Age at onset of pubertal milestones – Females										Age at onset of pubertal milestones – Males									
Demographic and clinical characteristics			Puberty		Growth		Body hair		Skin changes		Breasts		Menarche						
			β	SEM	β	SEM	β	SEM	β	SEM	β	SEM	β	SEM					
Age	-0.04 ^{ns}	0.08	-0.09 ^{ns}	0.07	0.03 ^{ns}	0.7	-0.09 ^{ns}	0.09	-0.05 ^{ns}	0.08	-0.07 ^{ns}	0.07	0.07						
Maternal age	-0.08 ^{ns}	0.06	-0.01 ^{ns}	0.06	-0.08 ^{ns}	0.05	-0.04 ^{ns}	0.07	-0.1 ^c	0.06	-0.02 ^{ns}	0.05	0.05						
Multiple gestation	0.3 ^{ns}	0.4	0.4 ^{ns}	0.4	0.2 ^{ns}	0.4	0.1 ^{ns}	0.5	-0.09 ^{ns}	0.4	-0.05 ^{ns}	0.3	0.3						
Low birthweight	0.2 ^{ns}	0.5	0.4 ^{ns}	0.5	0.06 ^{ns}	0.6	-0.9 ^{ns}	0.6	0.2 ^{ns}	0.5	0.05 ^{ns}	0.5	0.5						
Anovulation	0.09 ^{ns}	0.8	-0.1 ^{ns}	0.7	0.6 ^{ns}	0.7	1.1 ^{ns}	0.9	0.4 ^{ns}	0.8	0.8 ^{ns}	0.7	0.7						
Cervical/diethylstilbestrol/immunological	0.9 ^{ns}	0.8	1.5 ^b	0.7	1.0 ^{ns}	0.7	-0.2 ^{ns}	0.9	1.0 ^{ns}	0.8	0.8 ^{ns}	0.7	0.7						
Endometriosis	-0.6 ^{ns}	0.5	-0.8 ^{ns}	0.4	0.06 ^{ns}	0.5	-0.05 ^{ns}	0.5	-0.5 ^{ns}	0.5	-1.2 ^d	0.5	0.5						
Idiopathic	-1.4 ^{ns}	0.8	-0.1 ^{ns}	0.7	-0.4 ^{ns}	0.7	-1.6 ^{ns}	1.0	-0.2 ^{ns}	0.8	-1.1 ^{ns}	0.7	0.7						
Male	0.4 ^{ns}	0.5	0.8 ^{ns}	0.5	-0.2 ^{ns}	0.5	-0.3 ^{ns}	0.7	0.4 ^{ns}	0.5	0.5 ^{ns}	0.5	0.5						
Tubal	0.09 ^{ns}	0.4	-0.1 ^{ns}	0.3	-0.1 ^{ns}	0.3	0.2 ^{ns}	0.4	-0.3 ^{ns}	0.3	0.3 ^{ns}	0.3	0.3						

β = estimated slope coefficient for an ordinary least squares model that includes age at onset of a pubertal milestone as the dependent variable and a demographic or clinical characteristic as the independent variable; SEM=standard error of the mean;

ns = not significant;

^a $p=0.04$;

^b $p=0.03$;

^c $p=0.05$;

^d $p=0.009$.

Table 4

Age at onset of pubertal milestones as predictors of body size

	Weight (kg)			Height (m)			BMI (kg/m ²)		
	β (SEM)	P		β (SEM)	P		β (SEM)	P	
<i>Males and Females:</i>									
Puberty	0.8 (0.9)	0.3		0.02 (0.005)	0.002*		-0.2 (0.2)	0.2	
Growth	0.4 (0.7)	0.6		0.01 (0.004)	0.006*		-0.2 (0.2)	0.1	
Body hair	0.9 (0.8)	0.3		0.02 (0.005)	0.003*		-0.1 (0.2)	0.5	
Skin changes	1.3 (0.7)	0.07		0.01 (0.004)	0.02*		0.1 (0.2)	0.5	
<i>Males:</i>									
Puberty	-2.5 (1.4)	0.08		-0.007 (0.007)	0.3		-0.6 (0.4)	0.1	
Growth	-3.1 (1.0)	0.004*		-0.008 (0.005)	0.1		-0.7 (0.3)	0.02*	
Body hair	-1.7 (1.3)	0.2		-0.002 (0.006)	0.7		-0.4 (0.3)	0.2	
Skin changes	-1.8 (1.3)	0.2		-0.006 (0.006)	0.3		-0.4 (0.3)	0.3	
Voice changes	-2.4 (1.2)	0.05*		-0.005 (0.006)	0.4		-0.6 (0.3)	0.06*	
Facial hair	-1.9 (0.9)	0.04*		0.0003 (0.005)	0.9		-0.6 (0.2)	0.02*	
<i>Females:</i>									
Puberty	-0.5 (0.7)	0.5		0.006 (0.005)	0.2		-0.4 (0.2)	0.06	
Growth	-1.3 (0.8)	0.09		-0.0009 (0.005)	0.9		-0.5 (0.2)	0.04*	
Body hair	0.2 (0.8)	0.8		0.009 (0.005)	0.07		-0.2 (0.2)	0.3	
Skin changes	1.1 (0.6)	0.09		0.007 (0.004)	0.1		0.2 (0.2)	0.4	
Breast	-0.2 (0.7)	0.8		0.007 (0.005)	0.2		-0.3 (0.2)	0.1	
Menarche	-0.8 (0.8)	0.3		0.007 (0.005)	0.2		-0.5 (0.2)	0.03*	

β = estimated slope coefficient for an ordinary least squares model that includes body size as the dependent variable and age at onset of a pubertal milestone as the independent variable; BMI=body mass index; SEM=standard error of the mean.