The Indian Journal of Pediatrics
https://doi.org/10.1007/s12098-018-2822-x

REVIEW ARTICLE

Age at Menarche and Menstrual Abnormalities in Adolescence: Does it Matter? The Evidence from a Large Survey among Italian Secondary Schoolgirls

Vincenzo De Sanctis[1] · Franco Rigon[2] · Sergio Bernasconi[3] · Luigi Bianchin[4] · Gianni Bona[5] · Mauro Bozzola[6] · Fabio Buzi[7] · Carlo De Sanctis[8] · Giorgio Tonini[9] · Giorgio Radetti[10] · Egle Perissinotto[11]

Received: 16 October 2018 / Accepted: 16 November 2018

Abstract

Objective To explore the independent role of age at menarche on menstrual abnormalities among adolescents.

Methods The present study was a multicenter cross-sectional study on a large sample ($n = 3782$) of Italian girls aged 13–21 y attending secondary school who already had menarche. Girls were asked to fill in a questionnaire on menarcheal age and menstrual features during the latest three menses. The gynecological age was computed as the difference between age at the survey and the age at menarche. Main outcome measures were: prevalence of oligomenorrhea, polymenorrhea, menstrual cycle irregularity, abnormal bleeding length and dysmenorrhea. Irregularity in the recent past and since menarche was also studied. Multiple logistic models were used to identify any independent association between each abnormal feature and age at menarche or gynecological age. Adjusted ORs and 95%CI were performed.

Results After adjusting for covariates, menarcheal age was not independently associated with polymenorrhea (OR = 0.81; 95%CI 0.63–1.04), oligomenorrhea (OR = 1.16; 95%CI 0.94–1.43), menstrual cycle irregularity (OR = 0.99; 95%CI 0.86–1.14), abnormal bleeding length (OR = 0.96; 95%CI 0.87–1.06) and dysmenorrhea (OR = 1.03; 95%CI 0.85–1.24). The multivariate analysis suggests that the higher prevalence of oligomenorrhea and menstrual cycle irregularity among the girls who were older at menarche might be purely explained by their younger gynecological age.

Conclusions No evidence of any independent influence of age at menarche on menstrual abnormalities among young girls was shown by the investigation. The findings suggest that, after menarche, adolescent girls' menstrual health should be checked to monitor the endocrine system maturation and to early intercept latent disorders becoming symptomatic.

Keywords Age at menarche · Gynecological age · Menstrual irregularity · Menstrual pattern · Dysmenorrheal · Schoolgirls

✉ Egle Perissinotto
egle.perissinotto@unipd.it

[1] Private Accredited Hospital Quisisana, Pediatric and Adolescent Outpatients Clinic, Ferrara, Italy

[2] Department of Women's and Child Health, University of Padua, Padua, Italy

[3] Department of Pediatrics, University of Parma, Parma, Italy

[4] Child Psychiatric Unit, Local Health and Social Care Services - ULSS 6 Euganea, Padua, Italy

[5] Division of Pediatrics, Department of Mother and Child Health, Azienda Ospedaliero-Universitaria Maggiore della Carità, Novara, Italy

[6] Internal Medicine and Therapeutics, Section of Childhood and Adolescence, Foundation IRCCS San Matteo, University of Pavia, Pavia, Italy

[7] Department of Pediatrics, "Carlo Poma" Hospital, Mantova, Italy

[8] Department of Pediatric Endocrinology, Ospedale Infantile Regina Margherita, Turin, Italy

[9] University of Trieste, Trieste, Italy

[10] Department of Pediatrics, Regional Hospital of Bolzano, Bolzano, Italy

[11] Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Science and Public Health, University of Padua, Padua, Italy

Published online: 10 January 2019

Introduction

The menstrual cycle has been considered a marker of general health in adolescents [1]. Normal ovulatory menstrual cycles occur at regular intervals of 21 to 35 days and last for up to 7 d [2, 3]. Large prospective studies have demonstrated that 88–94% of menstrual bleeds last from 3 to 7 d during the first gynecological year [4].

Soon after menarche, the positive feedback response to estrogens that enables ovulation is frequently absent, so menstrual irregularity is common during this period. The hypothalamic-pituitary-ovarian (HPO) axis is not completely mature until five years after menarche [5], and anovulatory cycles are consequently common among young adolescents (up to 50% of cycles are anovulatory in the 1st year) [6]. Anovulatory bleeding may be indistinguishable from an ovulatory bleed, or it may be prolonged and excessive. As the HPO axis matures, a pattern of regular ovulatory cycles emerges and, within two years after menarche, adolescents generally have regular ovulatory cycles [7].

The purpose of monitoring of adolescents with menstrual dysfunction is to distinguish the irregular menstrual patterns typical of an immature HPO axis from the numerous anatomical and endocrine abnormalities that can occur in this age group, and that sometimes increase the risk of lasting menstrual abnormalities and reproductive disorders [8]. For instance, two in three of the girls whose oligomenorrhea persisted for more than 2 y still had oligomenorrhea 10 y later [9]. Wiksten-Almstrom̈er et al. [10] found that 59% of their sample of adolescents with persistent menstrual disorders met the criteria for the polycystic ovarian syndrome (PCOS). Women suffering from this condition are at high risk of developing long-term complications, including cardiovascular disease, type II diabetes mellitus, metabolic syndrome, and reproductive health problems [5, 11–14].

Females with later-onset menarche may not be fully ovulatory for 8–12 y after menarche [7, 15–17]. Vihko and Apter in 1984 claimed that frequency of ovulation depends largely on the time since menarche and age at menarche [7]. The time elapsing from menarche to the onset of regular menstrual cycles has been found significantly shorter for girls with early menarche (≤10 y) than for those whose menarche occurred late (≥15 y). Seventy two percent of the former and 63% of the latter experience regular cycles within 5 y after menarche and this would suggest that a later onset of menarche is accompanied by more persistent menstrual cycle irregularities [18]. On the other hand, recent data give the impression that there is no relationship between age at menarche and time to regularity in periods [19].

In the literature, the characteristics of girls' menstrual patterns have generally been related either to their age at menarche or to gynecological age, or to their chronological age. Widholm and colleagues in 1971 [20] suggested that gynecological age is the adequate basis also for comparison between girl's and mother's menstrual pattern.

To authors knowledge, no population-based studies in the literature have tested the independent role of age at menarche on menstrual disorders in adolescents considering relevant covariates.

This study sights to ascertain if age at menarche is independently associated with menstrual abnormalities on a large sample of adolescents attending secondary school.

Material and Methods

This cross-sectional multicenter study was conducted in 2000 on a large sample of Italian secondary school girls. Details of the sampling strategy used have been published elsewhere [21]. The girls were contacted at school and those who had reached menarche were recruited. This study was designed in accordance with the Helsinki Declaration; all participants were informed about the nature, purpose and procedures of the study, and informed written consent was obtained from the students and their legal guardians. According to the Italian regulations on observational research, the study was exempted from institutional ethics committee approval.

All information was obtained by means of a self-administered anonymous questionnaire. At each school, the local investigator described the aims of the survey and questionnaire to the science teachers, who then explained and distributed the questionnaire, supporting girls to filling in. Personal information was provided by the girls at school, while questions regarding their parents and siblings were answered at home together with their mothers.

The questionnaire was prepared and tested by pediatric endocrinologists and pediatric neuropsychiatrists at the Pediatrics Department of Padua University. As described previously [22, 23], it included questions on girls' demographics, anthropometrics, date of menarche, behavioral habits (smoking, alcohol consumption) and physical activity, their parents' socio-demographic data, and their mothers' and sisters' age at menarche and menses patterns.

The girls were asked to indicate their date of birth (day, month, year) and, as accurately as possible, the date of their first menstrual bleeding (at least the month and year; when the day was missing, it was assumed to be in the middle of the month). All ages were calculated in years: chronological age as the difference between the date of survey and the birth date; age at menarche as the difference between birth date and date of menarche, and gynecological age as the difference between age at menarche and chronological age.

Because of a limited number of cases in the analyses testing the relationships between age at menarche and menstrual abnormalities, girls who were ≤ 10 or ≥ 15 y old at menarche

were grouped together (early menstruation and late menstruation group, respectively) [22].

Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2). Socioeconomic status was determined using the Hollingshead Scale based on parental education and occupation at the time of the study.

Physical activity was measured as the number of hours per week spent performing any sports or physical exercise and was classified as follows: none-low = less than 2 h/wk.; moderate = 2–6 h/wk.; high = more than 6 h/wk.

Current smoking habit and alcohol consumption were recorded as dichotomous variables (yes/no), and current or past use of the contraceptive pill as a binary variable (yes/no).

For current menstrual cycle, features were recorded for the latest three menses in terms of: (i) duration of cycle [<21, 21–35, or > 35 d or irregular (without fixed length)]; (ii) mean days of bleeding (<4, 4–6, >6 d); (iii) menstrual pain (yes/no) and, if so, its duration (less than 1 d, for 1, 2, 3 d or more); (iv) use of pain medication (yes/no); (v) limitation of normal activities due to menses (yes/no).

The following types of menstrual disorders [24, 25] were defined: (i) oligomenorrhea, defined as intervals exceeding 35 d; (ii) polymenorrhea, defined as intervals of up to 21 d; (iii) menstrual cycle irregularity, *i.e.* menstrual cycles of variable duration; (iv) abnormal blood loss, defined as bleeding for more than 6 d.

Abdominal pain was ranked on four levels, as follows: no or mild/moderate abdominal pain; severe abdominal pain without any use of drugs, or sufficient to limit the girl's activities; severe abdominal pain treated with drugs, and/or activity limitations during bleeding days; severe abdominal pain treated with drugs and/or activity limitations before bleeding days (dysmenorrhea). In addition, data on the girls' previous experience of menstrual disorders were retrospectively collected through questions that allowed to identify oligomenorrhea/polymenorrhea in the past, menstrual irregularity in the recent past and since menarche.

All the analyses were performed with the SAS statistical software, rel. 9.1 (SAS Institute, Cary, NC, USA). The level of significance was set at 0.05 and all tests were two-tailed.

Descriptive analyses were performed on quantitative and qualitative variables for the total sample or for particular subgroups.

The normality of the quantitative variables was tested with the Shapiro-Wilk test. Differences between mean values were assessed by one-way analysis of variance, and age-adjusted p values were obtained by applying general linear models. The chi-squared test was used to compare proportions, and age-adjusted p values were obtained by means of multiple logistic models.

The relationship between a polynomial dependent variable (such as current duration of cycle or days of bleeding) and an independent variable (age at menarche or gynecological age), also adjusting for chronological age, was tested by applying polytomous logistic regression models.

Separate multiple logistic models were used to identify any independent association between each abnormal feature of menses as previously described and age at menarche or gynecological age. Covariates entered in the models were: age at the survey, BMI, family size, socioeconomic level, physical activity, smoking habit, alcohol consumption and contraceptive pill use. The goodness of fit was tested with the Hosmer-Lemeshow test. The goodness of fit of different models in predicting the same dependent variable was compared by means of the Akaike's information criterion and the Schwarz's Bayesian information criterion.

Results

Among 4,992 students who returned completed questionnaires, only 3,782 provided adequate information (date of birth and date of their first menses). The sample population had a mean age of 17.1 (±1.4) y old, with a mean BMI of 20.3 (± 2.5) kg/m^2. Mean age at menarche was 12.4 (±1.3) y and 95% of the study population had been between 10 and 15 y old at menarche.

About 62% of the girls belonged to families with high or very high socioeconomic levels and more than 51% exercised sports for more than 2 h/wk. About 30% of the sample were smokers, and 7.3% of the girls were habitual alcohol consumers (*i.e.*, they drank more than twice a week); 21% of them reported current/past use of the pill. Table 1 summarizes the menstrual pattern of the sample as a whole.

Table 2 shows the general characteristics of the sample grouped by age at menarche and gynecological age. Age at survey, BMI, socioeconomic level and physical activity were significantly different among age at menarche groups (p value <0.001 for the first two factors and 0.01 for the last two, respectively) and a younger age at menarche corresponded to an older gynecological age ($p < 0.001$).When the sample was grouped by gynecological age, the girls' age at survey, age at menarche, BMI, socioeconomic level, and level of physical activity differed significantly between the groups (all $p < 0.05$).

Table 3 shows the menstrual pattern by age at menarche and gynecological age. After adjusting for age at survey, an older age at menarche corresponded to significantly higher rates of oligomenorrhea ($p < 0.001$), menstrual cycle irregularity ($p < 0.001$), and lower rates of dysmenorrhea ($p = 0.02$). Gynecological age was associated with oligomenorrhea, menstrual cycle irregularity and dysmenorrhea, even though ever inversely with respect to age at menarche. The prevalence of oligomenorrhea and irregularity was significantly lower among the girls of older gynecological age ($p < 0.001$) while higher rates of dysmenorrhea were shown with increasing age ($p < 0.001$). No association emerged in age-adjusted analysis

Table 1 Menstrual features of secondary-school girls

	Sample population	
	n	%
Duration of cycle[a]	3539	
Polymenorrhea		
< 21 d	90	2.5
21–35 d	3024	85.5
Oligomenorrhea (> 35 d)	130	3.7
Irregularity	295	8.3
Polymenorrhea in the past (length < 21 d)	1131/3321	34.1
Oligomenorrhea in the past (length > 35 d)	1843/3457	53.3
Irregularity in the recent past[b]	1019/3655	27.9
Irregularity since menarche[c]	2531/3475	72.8
Days of bleeding	3761	
< 4 d	105	2.8
4–6 d	2918	77.6
> 6 d	738	19.6

[a] Polymenorrhea -Intervals of 21 d or less; Oligomenorrhea- intervals of 35 d or more; Irregularity - menstrual cycles of variable duration

[b] Answered 'no' to the question: 'Has the duration of your menstrual cycle usually (referring to the last three menses) stayed the same?'

[c] Answered 'no' to the question: 'Has the duration of your menstrual cycle always stayed the same?'

between the days of bleeding and either age at menarche or gynecological age.

The prevalence of menstrual cycles of normal duration (25–35 d) was significantly different ($p < 0.001$) depending on the time it was referred: as reported by the girls at the time of survey (85.5%), as they recalled for the recent past (72.1%), and for the past since menarche (27.2%) (Fig. 1). In any case, the prevalence of menses of normal duration significantly increased with gynecological age: from 71% to 90% at the time of survey (p for trend <0.001); from 56% to 83% in the recent past (p for trend <0.001); from 17% to 42% in the past (p for trend <0.001).

The results of simple and multiple logistic regressions testing the independent influence of age at menarche and gynecological age on any menstrual abnormalities are shown in Table 4. For each abnormal menstrual condition, age at menarche and gynecological age were entered separately or together in the multivariate logistic models (MLM1-MLM10 and MLM11-MLM15, respectively). Only gynecological age was found significantly and independently associated with all the conditions apart from bleeding for > 6 d, with older gynecological ages corresponding to fewer cycle abnormalities [OR 0.78 (95% CI 0.66–0.93) for polymenorrhea and 0.86 (0.73–0.99) for oligomenorrhea]. Contrarily, a positive association was observed between gynecological age and dysmenorrhea with OR 1.22 (1.07–1.41). The MLM2, MLM4,

Table 2 General characteristics by age at menarche and gynecological age

	Age at survey (years) Mean ± SD	Gynecological age (years) Mean ± SD	BMI (kg/m^2) Mean ± SD	Socioeconomic level[b] Mean ± SD	Physical activity (moderate-high) (%)	Smoking (%)	Alcohol consumption (> twice a week) (%)	Contraceptive pill use (%)
Age at menarche (years)								
≤ 10 (n = 480)	16.9 ± 1.5	6.6 ± 1.6	21.2 ± 2.9	9.3 ± 3.0	48.2	27.9	8.3	20.9
11 (n = 921)	17.1 ± 1.3	5.6 ± 1.4	20.7 ± 2.5	9.5 ± 3.1	50.1	32.0	7.3	20.2
12 (n = 1152)	17.0 ± 1.4	4.5 ± 1.4	20.2 ± 2.3	9.4 ± 3.1	53.0	28.6	7.1	22.2
13 (n = 864)	17.2 ± 1.4	3.8 ± 1.4	19.9 ± 2.3	9.5 ± 3.1	50.8	31.4	6.8	20.3
14 (n = 283)	17.4 ± 1.2	3.1 ± 1.2	19.7 ± 2.4	9.6 ± 3.1	54.4	32.2	7.1	22.6
≥ 15 (n = 86)	17.8 ± 1.3	2.1 ± 1.4	19.6 ± 2.4	10.5 ± 3.1	63.2	30.9	10.5	13.2
Significant p	<0.001	<0.001	<0.001[a]	0.01 [a]	0.01 [a]	0.88 [a]	0.56 [a]	0.21 [a]
Gynecological age (years)								
< 1 (n = 56)	14.7 ± 1.2	14.1 ± 1.1	19.5 ± 2.7	8.9 ± 2.9	64.3	16.1	3.6	7.1
1 (n = 163)	15.4 ± 1.2	13.8 ± 1.2	19.6 ± 2.7	9.9 ± 3.1	60.1	17.2	4.3	13.5
2 (n = 378)	15.9 ± 1.1	13.3 ± 1.1	19.9 ± 2.5	9.5 ± 2.9	56.6	22.8	6.6	15.9
3 (n = 709)	16.6 ± 1.0	13.0 ± 1.0	20.1 ± 2.4	9.5 ± 3.2	57.4	28.5	8.6	18.9
4 (n = 829)	17.1 ± 0.9	12.6 ± 0.9	20.3 ± 2.2	9.8 ± 3.1	53.6	31.1	6.2	20.6
5 (n = 811)	17.5 ± 1.0	12.0 ± 0.9	20.4 ± 2.3	9.5 ± 3.1	46.2	33.7	6.5	21.8
6 (n = 514)	18.0 ± 0.9	11.5 ± 0.9	20.9 ± 2.8	9.4 ± 3.1	46.7	33.9	9.7	24.9
7 (n = 193)	18.6 ± 0.1	11.1 ± 1.0	20.6 ± 2.7	9.0 ± 3.0	39.9	35.8	10.4	31.6
≥ 8 (n = 121)	19.3 ± 1.3	10.3 ± 1.2	22.0 ± 3.3	8.3 ± 3.1	42.2	38.0	6.6	37.2
Significant p	<0.001	<0.001 [a]	<0.001 [a]	0.04 [a]	0.01 [a]	0.45 [a]	0.51 [a]	0.09 [a]

Differences between mean values were assessed by one-way ANOVA, and age-adjusted p values were obtained by applying general linear models

[a] Adjusted for age at survey

[b] Socioeconomic level: 0 min, 16 max

Table 3 Prevalence (%) of menstrual cycle characteristics at time of survey by age at menarche and gynecological age

	Duration of menstrual cycle				Days of bleeding			Dysmenorrhea
	Polymenorrhea (< 21 d)	21–35 d	Oligomenorrhea (> 35 d)	Irregularity (no fixed length)	< 4 d	4–6 d	> 6 d	%
Age at menarche (years)								
≤ 10 (n = 480)	3.4	87.1	2.4	7.1	2.9	77.2	19.9	7.3
11 (n = 921)	2.3	87.5	3.1	7.1	2.7	78.3	19.0	5.8
12 (n = 1152)	2.2	86.7	3.0	8.2	2.6	78.1	19.3	5.0
13 (n = 864)	2.7	82.6	5.2	9.5	2.3	76.6	21.1	5.5
14 (n = 283)	2.6	84.5	4.2	8.7	4.3	76.8	18.9	4.0
≥ 15 (n = 86)	2.5	70.9	8.9	17.7	4.7	78.8	16.5	2.7
p value [a]	0.83	reference	<0.001	<0.001	0.58	reference	0.67	0.02[b]
Gynecological age (years)								
< 1 (n = 56)	5.9	70.6	9.8	13.7	3.6	76.8	19.6	2.0
1 (n = 163)	2.0	75.0	9.9	13.2	3.7	69.9	26.4	1.4
2 (n = 378)	2.1	81.7	3.6	12.6	2.4	78.4	19.2	4.3
3 (n = 709)	4.2	80.3	4.7	10.7	2.7	76.7	20.6	3.8
4 (n = 829)	2.6	88.0	2.8	6.6	2.0	78.6	19.5	5.4
5 (n = 811)	1.7	87.6	3.1	7.6	3.0	78.1	18.9	5.8
6 (n = 514)	1.8	89.0	3.1	6.1	3.1	76.9	20.0	*8.7*
7 (n = 193)	2.7	92.4	1.1	3.8	4.7	80.3	15.0	8.2
≥ 8 (n = 121)	1.7	89.7	2.6	6.0	2.5	79.8	17.7	6.7
p value [a]	0.65	reference	<0.001	<0.001	0.69	reference	0.47	<0.001[c]

[a] Adjusted for age at survey obtained by applying polytomous logistic regression models

[b] Adjusted for age at survey obtained by applying a multivariate binary logistic regression model

[c] Given that age at survey and gynecological age were markedly linearly correlated (r = 0.67; p < 0.0001), p was obtained by applying a simple binary logistic regression model

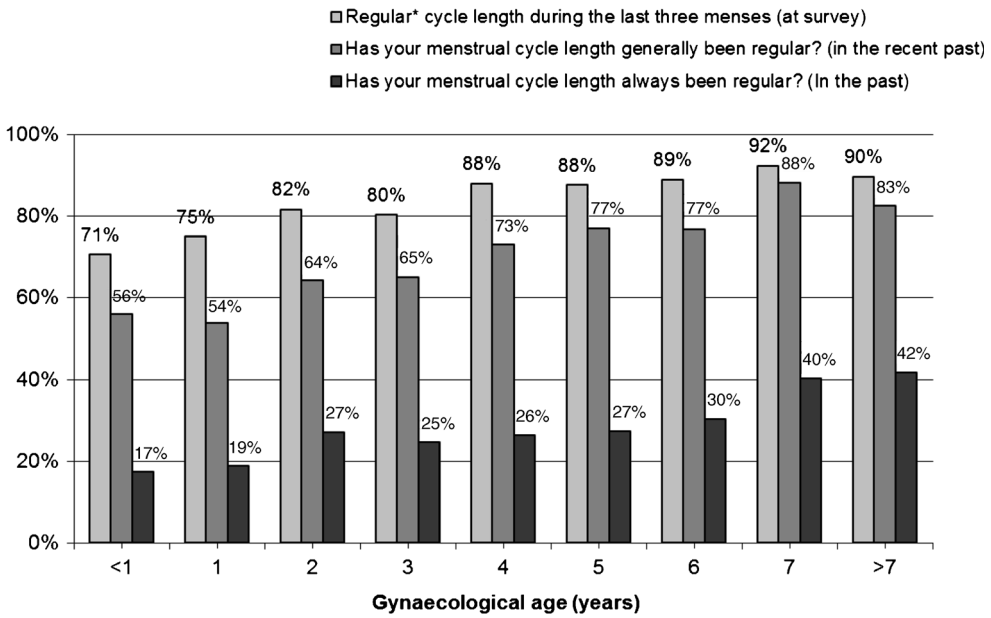

Fig. 1 Prevalence of regularity emerging from questions referring to the past and the time at survey

Table 4 Association between age at menarche and/or gynecological age and menstrual disorders

Menstrual disorders (dependent variable)	Age (years) (predictor)	ORs Simple logistic model (one predictor)	*p*	Multiple logistic model (MLM)	ORs Multiple logistic model[a] (one predictor)	*p*	Multiple logistic model (MLM)	ORs Multiple logistic model[b] (both predictors)	*p*
Polymenorrhea	At Menarche	0.97 (0.82–1.16)	0.77	1	1.03 (0.85–1.12)	0.75	11	0.81 (0.63–1.04)	0.10
	Gynecological	0.89 (0.79–1.00)	0.05	2	0.86 (0.74–0.98)	0.03		0.78 (0.66–0.93)	0.007
Oligomenorrhea	At Menarche	1.29 (1.11–1.48)	0.0006	3	1.35 (1.15–1.60)	0.0003	12	1.16 (0.94–1.43)	0.16
	Gynecological	0.81 (0.73–0.90)	<0.0001	4	0.80 (0.71–0.90)	0.0003		0.86 (0.73–0.99)	0.05
Irregularity	At Menarche	1.15 (1.04–1.26)	0.007	5	1.18 (1.03–1.32)	0.005	13	0.99 (0.86–1.14)	0.92
	Gynecological	0.83 (0.78–0.90)	<0.0001	6	0.84 (0.77–0.91)	<0.0001		0.84 (0.76–0.93)	0.0007
Days of bleeding > 6	At Menarche	1.01 (0.94–1.08)	0.86	7	1.02 (0.94–1.11)	0.60	14	0.96 (0.87–1.06)	0.43
	Gynecological	0.96 (0.91–1.01)	0.07	8	0.95 (0.90–1.01)	0.09		0.94 (0.87–1.01)	0.08
Dysmenorrhea	At Menarche	0.88 (0.78–1.00)	0.05	9	0.84 (0.72–0.97)	0.02	15	1.03 (0.85–1.24)	0.79
	Gynecological	1.21 (1.11–1.32)	<0.0001	10	1.21 (1.09–1.35)	0.0004		1.22 (1.07–1.41)	0.004

Covariates in the models MLM1-MLM6 were: BMI, family size, socioeconomic level, physical activity, alcohol consumption, smoking habit, physical activity, contraceptive pill use

Covariates in the models MLM7 and MLM8 were: BMI, family size, socioeconomic level, physical activity, alcohol consumption, smoking habit, physical activity, contraceptive pill use, menstrual irregularities

Covariates in the models MLM9 and MLM10 were: BMI, family size, socioeconomic level, physical activity, alcohol consumption, smoking habit, physical activity, contraceptive pill use, menstrual irregularities and bleeding

[a] Each menstrual abnormality was the dependent variable in separate simple and multiple logistic regression models. Menarcheal/gynecological age was separately entered as predictor in the multiple models, along with covariates. Chronological age was entered only in the models MLM1, MLM3, MLM5, MLM7 and MLM9

[b] Both menarcheal and gynecological age were entered together with the other covariates in the models MLM11-MLM15

MLM6, MLM8, MLM15 showed the lowest values both for Akaike's and the Schwarz's criteria (data not shown). For each model, the Hosmer-Lemeshow test confirmed a good fit (data not shown).

Discussion

In the literature, several surveys seem to suggest an independent effect of age at menarche on menstrual disorders. A few longitudinal studies on the independent role of age at menarche indicated that girls who start menstruating early tend to establish regular ovulatory cycles more rapidly than those whose menarche occurs later [7].

In the present cross-sectional population-based study, the independent influence of the age at menarche on menstrual abnormalities was tested using multivariable models. The results revealed that age at menarche is not independently associated with menstrual disorders.

About 13% of the present sample had an abnormally early menarche (up to 10 y old), and in 2% it came late (after 15 y old), as reported by other studies [1–8]. The prevalence of oligomenorrhea (2–3%) and the rates of irregular menstrual cycles (6%) among the present adolescents of oldest gynecological age (> 6 y) was consistent with the report from Rowland et al. [26] concerning a French adult population of 20- to 40-year-olds (about 3% and 5%, respectively). On the other hand, the prevalence of polymenorrhea in the present adolescents of oldest gynecological age was significantly lower than that among the French women (1–2% and 10%, respectively) but consistent with findings published by Anai et al. [16] concerning women aged 20 y (5%). In agreement with Anai et al. [16] and Widholm et al. [20], authors found girls with late menarche had a significantly higher prevalence of irregular menstrual cycles, oligomenorrhea, and polymenorrhea.

The prevalence of regular cycles among present adolescents (about 80%) was higher than that reported elsewhere in the literature, *e.g.* about 60% by the fifth year after menarche in a similar population [27], but the difference was smaller when considering regularity in the past. The present findings are comparable with those provided by Clavel-Chapelon et al., who used data retrospectively collected on a large cohort of French women, evoking that the figures depend largely on the question used to obtain this information [17].

In the present sample, the late-menstruating girls at survey had been no more than 1 y older (in chronological terms) than the early-menstruating girls at the time of their menarche. On the contrary, gynecological age differed significantly when girls were grouped by age at menarche, late menarche naturally coinciding with a significantly younger gynecological age. The multivariate analysis suggests that the higher prevalence of oligomenorrhea and menstrual cycle irregularity among the girls who were older at menarche might be purely explained by their younger gynecological age. It shows that age at menarche does not affect the prevalence of menstrual disorders in early reproductive life once gynecological age has been taken into account. Consistently, by stratifying subjects of comparable gynecological age, the analysis showed similar prevalence of disturbances for different age at menarche (data not shown). This would suggest that earlier post-menarche events are influenced mainly by the rate of maturation of the HPO system, while early or late menarche would have little influence on problems in early reproductive health. This may not necessarily be in contrast with evidence of an association between age at menarche and diseases later in life, by which time any lifelong endocrine or metabolic disorders (that might have influenced the girl's age at menarche) may have become apparent [28].

Notably, neither age at menarche nor gynecological age were significantly associated with excessive bleeding (> 6 d). In the literature, dysfunctional uterine bleeding (*i.e.* when there are no identifiable pathological conditions to explain the blood loss) has been associated with anovulation and consequent hormonal effects on the endometrium. The absence of any trend in gynecological age points to the hemodynamic system being implicated and affecting menstrual bleeding patterns (*e.g.* platelet or coagulation disorders could alter the hemostatic cascade).

Among the study's shortcomings, the self-reported menarcheal age might have been influenced by a memory bias, with older gynecological ages corresponding to lower accuracy. Actually, in that case, the error would have been symmetric (increasing or decreasing both menarche and gynecological age) and it would have lowered the strength of associations for both ages. Moreover, although the optimal design for a study on this issue would be a cohort study following girls from menarche up to at least 6 y later, robust results were allowed by the large size of this cross-sectional study. Additionally, the sampling strategy, the absence of exclusion criteria and the general characteristics of the sample population of this study support the generalizability of the findings to a population of secondary school adolescents.

In conclusion, this investigation provides no evidence of any major independent influence of age at menarche on menstrual abnormalities among adolescents. On the contrary, after menarche, adolescent girls' menstrual health should be checked to monitor the endocrine system maturation and to early intercept latent disorders becoming symptomatic.

Contributions CDS conception and design of the study, acquisition of data, revision of the paper. VDS conception of the scientific question and design of the study, acquisition of data, interpretation of data, revision of the paper. EP conception of the scientific question and design of the study, analysis and interpretation of data, draft and revision of the paper. GR conception and design of the study, acquisition of data, interpretation of data, revision of the paper. FR conception and design of the study, acquisition of data, interpretation of data, revision of the paper. EP will act as guarantor for this paper.

Compliance with Ethical Standards

Conflict of Interest None.

Source of Funding None.

References

1. American Academy of Pediatrics Committee on Adolescence, American College of Obstetricians and Gynecologists Committee on Adolescent Health Care, Diaz A, Laufer MR, Breech LL. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Pediatrics. 2006;118:2245–50.
2. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. Int J Fertil. 1967;12:77–126.
3. Vollman RF. The menstrual cycle. Major Probl Obstet Gynecol. 1977;7:1–193.
4. Flug D, Largo RH, Prader A. Menstrual patterns in adolescent Swiss girls: a longitudinal study. Ann Hum Biol. 1984;11:495–508.
5. Metcalf MG, Skidmore DS, Lowry GF, Mackenzie JA. Incidence of ovulation in the years after the menarche. J Endocrinol. 1983;97:213–9.
6. Mansfield MJ, Emans SJ. Adolescent menstrual irregularity. J Reprod Med. 1984;29:399–410.
7. Vihko R, Apter D. Endocrine characteristics of adolescent menstrual cycles: impact of early menarche. J Steroid Biochem. 1984;20:231–6.
8. Adams Hillard PJ. Menstruation in adolescents: what's normal, what's not. Ann N Y Acad Sci. 2008;1135:29–35.
9. Southam AL, Richart RM. The prognosis for adolescents with menstrual abnormalities. Am J Obstet Gynecol. 1966;94:637–45.
10. Wiksten-Almströmer M, Hirschberg AL, Hagenfeldt K. Menstrual disorders and associated factors among adolescent girls visiting a youth clinic. Acta Obstet Gynecol Scand. 2007;86:65–72.
11. Venturoli S, Porcu E, Flamigni C. Polycystic ovary syndrome. Curr Opin Pediatr. 1994;6:388–96.
12. Cheung LP, Ma RCW, Lam PM, et al. Cardiovascular risks and metabolic syndrome in Hong Kong Chinese women with polycystic ovary syndrome. Hum Reprod Oxf Engl. 2008;23:1431–8.
13. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997;18:774–800.
14. World Health Organization Task Force on Adolescent Reproductive Health. World Health Organization multicenter study on menstrual and ovulatory patterns in adolescent girls. II. Longitudinal study of menstrual patterns in the early postmenarcheal period, duration of bleeding episodes and menstrual cycles. J Adolesc Health Care. 1986;7:236–44.
15. Adams Hillard PJ, Nelson LM. Adolescent girls, the menstrual cycle, and bone health. J Pediatr Endocrinol Metab. 2003;16:673–81.
16. Anai T, Miyazaki F, Tomiyasu T, Matsuo T. Risk of irregular menstrual cycles and low peak bone mass during early adulthood associated with age at menarche. Pediatr Int. 2001;43:483–8.
17. Clavel-Chapelon F, E3N-EPIC Group. European Prospective Investigation into Cancer. Evolution of age at menarche and at onset of regular cycling in a large cohort of French women. Hum Reprod. 2002;17:228–32.
18. Hosokawa M, Imazeki S, Mizunuma H, Kubota T, Hayashi K. Secular trends in age at menarche and time to establish regular menstrual cycling in Japanese women born between 1930 and 1985. BMC Womens Health. 2012;12:19.
19. Dossus L, Kvaskoff M, Bijon A, et al. Determinants of age at menarche and time to menstrual cycle regularity in the French E3N cohort. Ann Epidemiol. 2012;22:723–30.
20. Widholm O, Kantero RL. A statistical analysis of the menstrual patterns of 8,000 Finnish girls and their mothers. Acta Obstet Gynecol Scand Suppl. 1971;14:1–36.
21. Rigon F, Bianchin L, Bernasconi S, et al. Update on age at menarche in Italy: toward the leveling off of the secular trend. J Adolesc Health. 2010;46:238–44.
22. Rigon F, De Sanctis V, Bernasconi S, et al. Menstrual pattern and menstrual disorders among adolescents: an update of the Italian data. Ital J Pediatr. 2012;38:38.
23. De Sanctis V, Bernasconi S, Bianchin L, et al. Onset of menstrual cycle and menses features among secondary school girls in Italy: a questionnaire study on 3,783 students. Indian J Endocrinol Metab. 2014;18:S84–92.
24. Kvåle G. Reproductive factors in breast cancer epidemiology. Acta Oncol Stockh Swed. 1992;31:187–94.
25. Dossus L, Allen N, Kaaks R, et al. Reproductive risk factors and endometrial cancer: the European prospective investigation into cancer and nutrition. Int J Cancer. 2010;127:442–51.
26. Rowland AS, Baird DD, Long S, et al. Influence of medical conditions and lifestyle factors on the menstrual cycle. Epidemiol Camb Mass. 2002;13:668–74.
27. Järvelaid M. The effect of gynecologic age, body mass index and psychosocial environment on menstrual regularity among teenaged females. Acta Obstet Gynecol Scand. 2005;84:645–9.
28. Kivimäki M, Lawlor DA, Smith GD, et al. Association of age at menarche with cardiovascular risk factors, vascular structure, and function in adulthood: the cardiovascular risk in young Finns study. Am J Clin Nutr. 2008;87:1876–82.