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Original Study

Elevated Testosterone and Hypergonadotropism in Active Adolescents of Normal Weight with Oligomenorrhea

K. Singer, MD, MA, A. Rosenthal, MD, and J. Kasa-Vubu, MD, MS
Department of Pediatrics, University of Michigan, Ann Arbor Michigan

Abstract. *Study Objective:* Oligomenorrhea in active adolescent females of normal weight is presumed to be related to hypoestrogenism secondary to physical activity and decreased fat mass. We hypothesized that active adolescents with oligomenorrhea would have lower estrogen levels than normal controls with similar levels of cardiovascular fitness.

Design/Participants: Twenty healthy participants between the ages of 16 and 20 years were recruited at least 2 years postmenarche. Adolescents reporting fewer than 9 cycles a year (n = 6) were compared to 14 controls with monthly menstrual cycles. Histories of eating disorder, hirsutism, severe acne, depression, or amenorrhea were cause for exclusion.

Main Outcome Measures: Body composition and bone density were measured by total body dual x-ray absorpitometry. Cardiovascular fitness was evaluated by measuring oxygen consumption during exercise. Control subjects were matched by age, body mass index (BMI), and fitness level. Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, progesterone, and estradiol were obtained. Statistical analysis was performed using SAS 9.1.

Results: Cardiovascular fitness in both groups was within normal limits for age. No significant differences in BMI, estradiol concentrations, or bone density were found, but trunk fat mass was lower in adolescents with oligomenorrhea who also reported more frequent exercise. Testosterone concentrations and LH/FSH ratios were significantly higher in participants with irregular menstrual cycles ($P = 0.0018$ and < 0.001, respectively).

Conclusion: Adolescents with oligomenorrhea were leaner, yet they had higher testosterone levels and a greater LH/FSH ratio than their BMI-matched, cyclic counterparts. We hypothesize that, in active adolescents of normal weight, elevated androgen and LH concentrations are linked to ovarian dysfunction, which can masquerade as exercise-induced oligomenorrhea.

Key Words. Oligomenorrhea—Androgen—Fitness

Introduction

Oligomenorrhea during adolescence is closely linked to weight and activity status. Irregular menses are linked to competitive exercise and low estrogen levels in lean adolescents[1–3] and are also linked to sedentary behavior and high androgen levels in obese young women[4]. Therefore, oligomenorrhea in the active adolescent female of normal weight and without clinical evidence of androgen excess represents a diagnostic dilemma. Studies have examined oligomenorrhea and endocrine disruptions related to weight loss or energy deficits, but little is known within the context of moderate activity and normal weight.

Identification of the underlying cause of oligomenorrhea has important implications related to future fertility and long-term bone health.[5–7] Many studies focused on oligomenorrhea have examined menstrual pathophysiology in either underweight or obese women. Indeed, both ends of the weight spectrum represent an increased risk for menstrual irregularities in young women,[8,9] with exercise-induced amenorrhea and polycystic ovary syndrome (PCOS) representing the lean and obese extremes, respectively. The association of oligomenorrhea with moderate to intense physical activity is central to the evaluation of young women with menstrual irregularities.[10] The presumption of subclinical hypoestrogenism in lean and active adolescent women has been the basis for widespread use of hormonal means of birth control to compensate for this hypothetical hormonal deficiency, normalize the menstrual cycle, and optimize long-term bone

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Address correspondence to: Josephine Z. Kasa-Vubu, MD, MS, Department of Pediatrics, Division of Pediatric Endocrinology, University of Michigan Medical Center, Medical Professional Building, Ann Arbor, MI 48109-0718; E-mail: jzkv@umich.edu

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health.[11,12] However, irregular menses associated with normal weight and moderate physical activity have not been the focus of investigation. We sought to recruit active adolescent girls of normal weight engaged in noncompetitive moderate physical activity and mirroring as a group the normal fitness spectrum for this age. We tested the hypothesis that active adolescent girls with oligomenorrhea share a hormonal profile consistent with exercise-induced amenorrhea and would have lower estrogen levels than their cyclic counterparts.

Subjects

This protocol was approved by the Institutional Review Board of the University of Michigan Health System. We recruited 20 participants between the ages of 16 and 20 years, including 6 with oligomenorrhea (fewer than 9 menstrual cycles per year). In addition, 14 healthy controls were recruited; they had histories of regular menstrual cycles, averaging more than 10 cycles per year. All participants had body mass indexes (BMIs) between the 25^{th} and 75^{th} percentile for age (Centers for Disease Control Growth Charts from the National Center for Health Statistics). Participants were recruited from the local university campuses and gymnasiums and the university hospital. Inclusion criteria included history of normal age of menarche and a gynecological age (calculated from the reported age at menarche) of at least 2 years. Participants were taking no medications and no hormonal preparations and had no histories of pregnancy. A history of eating disorder, hirsutism,[13] severe acne, depression, or amenorrhea was a cause for exclusion by an initial questionnaire. In addition to the initial screen for exclusion criteria, a prospective 3-day food diary was collected after enrollment and was analyzed by the Clinical Research Center dietitian to screen for aberrant eating patterns, and none were detected. All participants were questioned about physical activity to determine how many hours per week were dedicated to voluntary exercise.

Methods

To standardize the window of time for sample collection, cyclic participants were instructed to contact the investigators by E-mail or by phone on the very first day of the menstrual cycle in order to schedule hormone data during the follicular phase (average cycle day for blood sampling 5.8 ± 0.7). Girls with oligomenorrhea where studied at random but the serum progesterone was drawn in all participants to confirm follicular phase status. Urine pregnancy testing was also performed for all subjects prior to enrollment into the study. Determination of the levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, dehydroepiandrosterone sulfate (DHEAS), progesterone, and estrogen was achieved with the use of commercial assays as described previously.[14] The LH/FSH ratio was calculated as a measure of hypergonadotropism, which can be associated with oligomenorrhea in adolescent girls.[7,8] Serum DHEAS was measured only in participants with oligomenorrhea.

Fitness Testing. We assessed fitness in two ways. First, by self-report of the number of hours of recreational or voluntary exercise per week. Second, by the measure of maximal aerobic capacity (VO_2max) determined by a treadmill test according to the Bruce Protocol, as described elsewhere.[15,16]

Body Composition. Body composition and body fat were obtained by dual x-ray absorptiometry (DEXA) using a total-body scanner. The DEXA scan provided both total and segmental data for body fat from which trunk fat mass was selected as a surrogate measure for central adiposity.

Data and Statistical Analysis. The results are all expressed as mean ± standard error unless indicated otherwise. All variables of interest were compared between groups using Student's *t*-test, including BMI, gynecological age, chronological age, bone mineral density, percent body fat, trunk fat mass, VO_2max, and hormone concentrations. Statistical analysis was performed using SAS version 9.1 software.

Table 1. Subjects' characteristics

	Regular Menses (n=14)	Irregular Menses (n=6)	P value
BMI (kg/m^2)	24.3 (1.4)	21.3 (0.8)	0.2
Age (years)	18.3 (0.5)	18.7 (0.2)	0.4
Gynecologic age (years)	5.8 (0.6)	5.5 (0.8)	0.7
Weekly exercise (hr/week)	2.1 (0.5)	4.3 (0.3)	0.002*
VO_2max (ml/kg·min)	37.8 (1.8)	41.2 (2.6)	0.3

BMI, Body mass index; VO_2max, maximal oxygen consumption.

Results

Subjects' characteristics are described in Table 1. There were no statistically significant differences for BMI, age, or gynecological age between the cyclic and the oligomenorrheic groups. The average BMI was within the 25^{th} to 75^{th} percentile for age and sex in both groups. Cardiovascular fitness relative to body mass was similar in both groups and within the normal range for age.[15] However, participants with oligomenorrhea reported increased number of hours per week of exercise ($P < 0.01$).

As shown in Table 2, DEXA analysis revealed that participants with regular menses and irregular menses