GROWTH AND MATURATION IN HUMAN BIOLOGY AND SPORTS

FESTSCHRIFT HONORING ROBERT M. MALINA BY FELLOWS AND COLLEAGUES

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AGE AT MENARCHE IN ATHLETES: INTERACTIONS AMONG CENTRAL MECHANISMS

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INTRODUCTION

It is indeed and honor and privilege to dedicate this chapter to Robert. M. Malina, Ph.D. I have chosen a subject upon which Bob has written extensively; that of menarche in athletes. Rather than take the "usual" approach and just catalog the age at menarche in various sports and the sub-disciplines within them (many, including himself, have done that extensively), he has taken the scientific/sociologic approach noting that these are young women first, and then athletes. He has extensively studied the effects of sibship, birth order, socio-economic class, etc, as covariates for the training time (volume), and intensity of that training [as reviewed in (Malina, *et al*, 2004)].

I shall not merely point out the multiple studies that Bob has done or reviewed, but shall emphasize the great variability of age at menarche among all adolescents before moving to an experimental basis likely accounting for secondary amenorrhea among adolescent athletes. The latter because it likely informs us about menarche as well, although this pivotal event in an adolescent girl's life has not been as extensively studied. I shall end with some more speculative findings in the discipline of hypogonadotropic hypogonadism, for the data presented point to variability in genes than affect both gonadotropin-releasing hormone (GnRH) physiology and the hypothalamic regulation of appetite. An intriguing hypothesis is that any variety of stress, in this case high energy exercise in the presence of diminished eating, and perhaps activation of the hypothalamic-pituitary-adrenal axis, may have an intensified effect on the reproductive axis (luteal phase defect and secondary amenorrhea, and by analogy, primary amenorrhea) in those women with heterozygous alterations in one of the several affected genes (Mitchell, *et al*, 2011; Caronia, *et al*, 2011).

Data for the age at menarche are simply descriptive (McIntyre and Kacerosky, 2011). They do account for variability within the specific group studied without attribution for the breadth of that variability. It should be noted that menarche is a very late event within pubertal maturation, lagging by several years the re-initiation of pulsatile GnRH (and thus luteinizing hormone, LH) secretion, the phases of follicular development, the growth spurt and external indicators of adolescent maturation-breasts and the addition and redistribution of body fat. Although puberty progresses in an orderly fashion, there is much variability in its onset, progression and completion (beyond menarche). However, once entrained the variability between stages (*tempo)*, although still present, is less. Most girls

will experience menarche between 2 and 2.5 years after breast budding, although some of those having breast budding early will have a more desultory progression to menarche (Styne & Grumbach, 2004). They may show breast budding 2 or 3 years earlier than average, but menarche only a few months before the median age of menarche for that ethnic/racial group (Rosenfield, 2009)

Utilizing data from the mid-1970's to the mid-1990's, as summarized by Malina, et al (2004) the median age at menarche for North American girls was approximately 12.4 years with a breakdown of 12.1 years for Blacks, 12.5 years for Mexican-Americans, and 12.6 years for Whites. These are reference data from extensive cohorts obtained from multiple National Health and Nutrition Examination Surveys (NHANES) studies and individual studies such as the Bogalusa Heart Study (Anderson, *et* al, 2003; Freedman, *et* al, 2002; Wattigney *et* al, 1999). Within Europe there is an extensive north-south gradient with median ages at menarche varying from 12.7 to 13 years in Sweden to 12.4 to 12.7 years in Italy [summarized in Malina, et al (2004)].

Over the past 150 years there has been a secular trend for the lowering of age at menarche moving from approximately 17 years to a relative plateau over the past 50 years, at least in the more developed portions of the world, of about 12.5 years (Wyshak & Frisch, 1982, Wattigney, *et al*, 1999). There are likely multiple and intertwining reasons for this decline and they include better nutrition and clean water, eradication of many infectious diseases, and improvements in overall health status. The psychological impact of earlier maturation has not been well studied, but there is seemingly a greater disparity between physical maturation and social/emotional development, recently (Hillard, 2008). In addition there is the potential for adverse health consequences on conditions such as breast cancer.

AGE AT MENARCHE IN ATHLETES

Professor Malina has extensively studied and written about this subject from the methodologic (prospective or longitudinal; *status quo*; and the retrospective) point of view. The first two are to be desired, but often do not account for the "elite" status in many younger girls or those who drop out during the trajectory toward elite status—thus having bias toward those adolescents who continue to train at high levels of energy expenditure. The retrospective sets of data are most prominent, for these studies are the "easiest" to perform, but have the potential for error of recall, likely greater the longer the time interval between the event (menarche) and when the adolescent is asked for the date of menarche. It may prove useful in such studies to corroborate the date with the athlete's mother.

A snapshot summary has been presented by Malina et al (2004) showing the median and 95 % confidence intervals for non-athletes in the studies reviewed (13.0 ± 1.0 years) with 95 % CI (11.0 to 15.0 years). Athletes in various sports are compared against that background with the greatest delays in gymnasts and ballet dancers and perhaps, slight

acceleration in rowers and track and field athletes. These are of course global reference estimates without breaking down individual disciplines within, for example, track and field. As expected the aesthetic sports where high volumes of exercise are paired with diminished nutrient intake to satisfy the linear physic expected, for example ballet and diving, show on average, the greatest delay in menarcheal age. As noted by Malina, et al (2004) the sample sizes of adolescent athletes are generally small.

Longitudinal studies have even smaller numbers of girls and are potentially confounded by selective exclusion or drop out begging the question of selection for later maturing girls (more below re: gymnasts) or whether earlier maturing adolescents selectively drop out of gymnastics, ballet and other aesthetic sports. For example, artistic gymnastics is so selective that the elite athletes may approximate 0.1 % of those that partake in the sport [Malina, *et al.,* 2011]. Adolescents who compete at the International level are very significantly smaller and lighter than those of non-elite status and even more so compared to a non-athletic cohort. However, one must consider many more attributes of these elite adolescent athletes - their parents are shorter than average and the girls themselves are shorter than average for their age even before they began to train (Malina, *et al*, 2011). The growth and maturity characteristics differ among those who persist in the sport and those who drop out. Summarizing four small cohorts of female artistic gymnasts from Poland, Switzerland, Belgium, and Canada (Malina, *et al*, 2011; Claessens, *et al*, 1999; Roupas & Georgopoulos, 2011) found that girls who persisted in their training and competition were shorter on average at 12-15 years than those who dropped out. In contrast those who persisted were lighter throughout the age range. Those who persisted with training, reached peak height velocity late and attained menarche only slightly later; however, the sample sizes were very small.

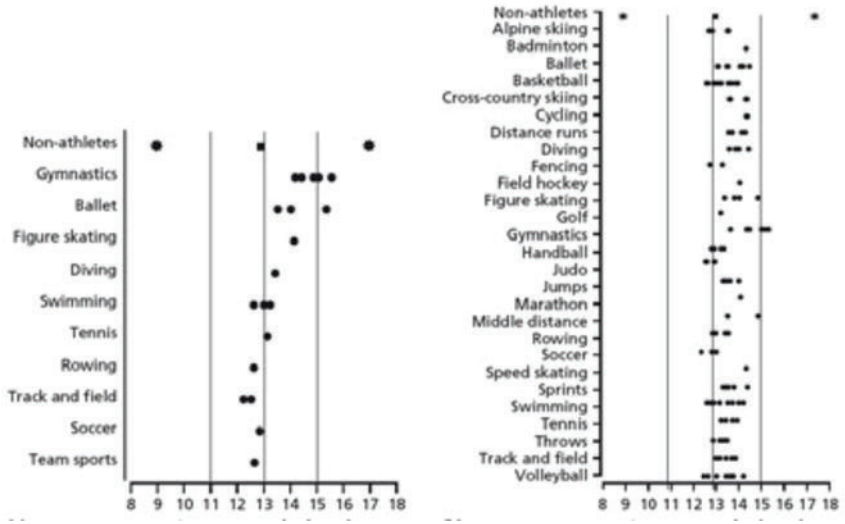

Figure 1. Mean ages at menarche in adolescent athletes grouped by sport: longitudinal and status quo studies (left), retrospective studies (right).

HYPOTHALAMIC-PITUITARY-GONADAL (HPG) AXIS

The hypothalamic-pituitary-gonadal axis is active during the latter two-thirds of fetal life in both sexes. At birth the abrupt disconnection of the placenta markedly diminishes the levels of placental-derived estrogens with immediate consequences of these lower levels on the hypothalamus and pituitary. During neonatal/infancy maturation in boys there is a well-described pattern of gonadotropin [predominantly luteinizing hormone (LH)] and testosterone levels. The previously suppressed gonadotropins [LH and follicle-stimulating hormone (FSH)] are suddenly released from negative feedback as estradiol levels decrease from birth. During the first few weeks of life LH and FSH levels increase followed by an increase in testosterone over approximately the first 12 weeks of life. This "mini-puberty" wanes to be followed by the juvenile "hiatus", which itself ends with the onset of pubertal maturation (Fuqua & Rogol, 2011).

The mean level of FSH is clearly higher in the female and remains elevated over the childhood baseline for approximately 2 years. The consequences of this are raised levels of estradiol. It is at these times (6-24 months) that girls may have thelarche (appearance of glandular breast tissue), which regresses after the second year and remains

"suppressed" until the re-awakening of the HPG axis as pubertal maturation unfolds (Fuqua & Rogol, 2011).

The first external sign of physiological puberty is most often thelarche. For this to occur there had to have been a re-awakening of the HPG axis where the very low concentrations of estradiol are no longer capable to restrain the pulsatile release of GnRH. The pituitary is sensitive to the frequency and amplitude of these GnRH pulses and responds with pulsatile LH and FSH release, the composition of the mixture depending on the frequency of the GnRH pattern (Fuqua & Rogol, 2011).

It is intriguing to note an inverse relationship between low birth weight and age of pubertal onset as well as menarche. In those with low birth weight, but subsequently become obese (BMI > 95th centile) menarche is advanced by approximately 6 months (McCartney, *et al*, 2009).

Luteinizing hormone induces the follicle to produce precursors to estradiol whereas FSH induces the enzyme aromatase to synthesize these precursors (androgens) into estrogens. Menarche occurs at least a year beyond continuously increasing estradiol levels and likely an alteration in negative feedback on the hypothalamus permitting a small window of positive feedback [increasing levels of estradiol lead to increases in LH secretion (ovulatory spike)], ovulation, and the formation of the corpus luteum. Obesity has an effect on the reproductive axis by perhaps having an earlier start of puberty, but often a not so early menarche given the higher levels of testosterone and lower levels of sex hormone-binding globulin, yielding higher levels of free (biologically active) testosterone (McCartney, *et al*, 2009). Just the opposite occurs with the thin athletes with a later start of activation of the HPG axis and the nutritionally-activated signals. This leads directly to an interaction of the signals of the HPG axis and those of appetite (satiety) as noted below.

APPETITE-SATIETY

Regulation of body weight is a precise, clearly complex, process that keeps caloric intake balanced to expenditure within an error range of approximately 1.25 % (Yanovsky, et al, 2000). There are a series of inputs into the central nervous system, likely integrated in multiple nuclei of the hypothalamus. These signals are hormonal, metabolic and neuronal and detect and alter the delicate balance of total energy to permit normal physiologic function (including reproduction) and body weight over years and decades. For women the issue of reproductive competence is closely allied with the total energy balance. A woman can survive famine more easily, if she is not reproductively competent. If the reproductive system can be dampened only to reawaken at times of positive overall energy balance, this is salutary for preservation of the species - fecundity during times of nutritional adequacy and infertility during times of critical caloric availability (van der Walt, *et* al, 1978).

This is clearly the case for the hunter-gatherers of the northwestern Kalahari Desert (van der Walt, *et al*, 1978). It is only recently that some of the neuroendocrine mechanisms have been unraveled. Functional hypothalamic amenorrhea (FHA) and its subset in athletes are characterized by hypoestrogenemia, in the presence of low or normal concentrations of gonadotropins without any known (medical) cause. Athletes with FHA are of low body weight, obtain sub-balance amounts of nutrients and exercise extensively (Chou, *et al*, 2011). As expected for their low subcutaneous fat mass, the leptin levels are low. Although the balance of orexigenic (for example, NPY acting through PYY receptors and anorexigenic hormones (for example, pro-opiomelanocortin, POMC) should be tilted toward food intake, these women do not increase their caloric intake to balance the energy output (Russell, *et al*, 2011).

LEPTIN DEFICIENCY

Children with congenital leptin or leptin receptor deficiency are stark examples of the importance of leptin action for energy balance. Girls with either gene deficiency (*LEP* or *LEPR*) are markedly obese even within the first year of life and have delayed puberty in the second decade. Leptin treatment of girls with *LEP* deficiency markedly alters the appetite, permits significant weight loss and entry ("permissive") and progression through puberty (Farooqi, *et al*, 1999, 2007). More recent data noting central action on appetite centers are summarized by Farooqi (2010).

Leptin activates the POMC neurons and inhibits Agouti-related peptide (AgRP)/NPY neurons within the arcuate nucleus of the hypothalamus to stimulate feeding—in fact this has been shown in female runners with HA—infusions of leptin (Welt, *et al*, 2004) or chronic administration of metreleptin (a longer-acting analog of leptin) have reversed HA in some of the athletes (Chou, *et al*, 2011). Loucks and colleagues have noted that the HPG axis of adolescents (younger gynecological age) is more susceptible to net energy decrements than in the gynecologically older woman (Loucks, *et al*, 2006).

OVARIAN CYCLES AND HYPOTHALAMIC AMENORRHEA

Thus, it does not seem such a leap of logic to suspect that the very early ovarian cycles of the pre-menarcheal adolescent may be quite sensitive to the combination of high energy expenditure, sub-sufficient caloric intake, and stress which might delay (or prolong) adolescent maturation, including menarche. Additionally, many elite artistic gymnasts, for example, conform to the growth and maturational characteristics of short, delayed girls [and their families (Malina, *et al,* 2011)]. It is not so surprising that these adolescent athletes may have the greatest delay in their maturational trajectory.

An additional factor may involve mutations in genes that control energy balance and the HPG axis. One might consider the genes which in their homozygous form cause idiopathic hypogonadotropic hypogonadism (IHH) - that is, permanent HH (Mitchell, *et al*, 2011) may in their heterozygous form delay menarche or increase the susceptibility to environmental factors that might lead to FHA (Carmina, et al, 2011). In a group of women with HA (N=55) including some who exercised more than 5 hr/week, weight loss and subclinical eating disorders, 7/55 (13%) were noted to have heterozygous mutations in a number of genes, fibroblast growth factor 1 receptor (*FGFR1*), prokineticin receptor 2 (*PROKR2*), Kallmann syndrome 1 sequence (*KAL 1*) GnRH receptor 1 (*GNRHR*). No mutations were found in 422 control women with normal menstrual cycles (Carmina, *et al*, 2011). These genes play fundamental roles in GnRH ontogeny and physiology including alterations in the pulsatile release of GnRH. Several of these, for example, *FGFR 1* (Sun, *et* al, 2007) and *PROKR 2* (Gardiner, *et al*, 2010) signaling also affect eating behavior, at least in mice.

An intriguing hypothesis that may account for many of these findings is that the delayed menarche in some of the adolescent athletes is due to a combination of genetic factors leading to a small, delayed maturational phenotype and low caloric intake, and the stress of training and competition perhaps modified by heterozygous alterations in a small subset of genes that affect hypothalamic function for GnRH physiology and energy balance. Whatever the predominant reasons for delayed menarche in adolescent athletes, it is clear that it is not a single cause and likely a series of causes, individual to each adolescent.

SUMMARY

What has Bob Malina taught me about the subject of age at menarche in athletes? It is to use the scientific method to tease out other (perhaps confounding) factors within the girl/adolescent athlete that might affect the simple relationship of athletic training/competition, however quantitated. His insight into the sociological and psycho/social aspects of the young woman's life is merely his way of making a very simple statement: the athlete is a girl/adolescent first with the sum total of her genetics and daily/family life upon which her athletic training/competition is superimposed.

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