

Menarche is Related to Fat Distribution

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ABSTRACT The energy demands of pregnancy and lactation together with the accumulation of stored fat in human females during development suggest that a critical level of fat may be required for menarche; but multivariate analyses have supported the alternative view that skeletal growth is the main factor. However, significant differences between upper- and lower-body (gluteofemoral) fat suggest that fat distribution may be more relevant than total fat. Using cross-sectional data from the third National Health and Nutrition Examination Survey (NHANES III) for females aged 10–14, we show that menarche is more closely related to fat distribution than to skeletal maturity. Unit increases in hip circumference are associated with 24% higher odds of menarche while increases in waist circumference and triceps

skinfold lower the odds by 7 and 9%, respectively. Those with menarche despite low levels of total body fat have relatively more fat stored in gluteofemoral depots than those without menarche or those with menarche and greater total amounts of fat. In young women with completed growth, age at menarche is negatively related to hip and thigh circumference and positively related to waist circumference, stature, and biiliac breadth; and blood leptin levels are much more strongly related to gluteofemoral than upper-body fat, suggesting that leptin may convey information about fat distribution to the hypothalamus during puberty. Fat distribution may be relevant because gluteofemoral fat may provide neurodevelopmentally important fatty acid reserves. *Am J Phys Anthropol* 000:000–000, 2007. © 2007 Wiley-Liss, Inc.

Menarche is an important landmark in a woman's reproductive career; and, to the degree that selection molds the life-history of a species, one would expect sexual maturation to be linked to the acquisition of resources necessary for successful reproduction. The proximate cause of menarche is an increase in the frequency of the gonadotropin releasing hormone (GnRH) pulse generator in the hypothalamus, but the age at menarche varies widely and is delayed in populations with poor nutrition (Thomas et al., 2001; Gluckman and Hanson, 2006). Until recently it was generally accepted that the timing of menarche is related to skeletal growth, which comes about 1 year after the peak in height velocity (Simmons and Greulich, 1943; Elizondo, 1992).

An alternative view is that menarche depends on a critical amount of stored fat, since the 16 kg of fat typically stored during childhood and puberty can provide additional energy during pregnancy and lactation (Frisch and Revelle, 1970; Frisch and McArthur, 1974; Frisch et al., 1973; Frisch, 1976, 1994). The hormone leptin, produced by fat cells, provides a pathway to communicate the size of fat stores to the GnRH secreting neurons in the hypothalamus via leptin receptors in KiSS-1 neurons (Smith et al., 2006). Leptin is required for puberty (Chehab et al., 1996, 1997; Clement et al., 1998; Ozato et al., 1999; Farooqi et al., 2002), and age at menarche in young women is inversely related to leptin levels (Matkovic et al., 1997), with a significant 28% increase in leptin levels during the 6 months preceding menarche (Blogowska et al., 2005).

Despite the appeal of this hypothesis, studies of menarche have generally failed to support the critical-fat theory. Menarche can occur despite low fat levels with little evidence of a threshold (Johnston et al., 1971; Billewicz et al., 1976; Trussell, 1978; Garn and LaVelle, 1983); and multivariate analyses have shown that height and biiliac breadth are much more important than measures of total fat or body weight in predicting the age of

menarche (van't Hof and Roede, 1977; Ellison, 1982; Stark et al., 1989; Elizondo, 1992).

However, another possibility is that menarche may be related to fat distribution rather than total fat, and in particular to the relative amount of lower-body (gluteofemoral) vs. upper-body fat. Female waist-hip ratio (WHR) declines during childhood from 1.03 at 4 months of age to 0.78 at the time of menarche (Fredriks et al., 2005), and there is a steep increase in hip circumference just before menarche (Forbes, 1992). Young German women in higher quartiles for self-reported hip, thigh, and leg circumferences had higher odds of menarche in cross-sectional bivariate analyses (Merzenich et al., 1993).

There is also evidence that gluteofemoral fat produces more leptin than upper-body fat. Subcutaneous gluteal fat contains more leptin mRNA than abdominal fat (Papaspyrou-Rao et al., 1997), and multivariate analyses indicate that hip circumference is a significant positive predictor of blood leptin levels while waist circumference is not (Bennett et al., 1997; Ho et al., 1999; Sudi et al., 2000). For example, in the study by Bennett et al. (1997), hip circumference explained 36% of the variance in blood leptin levels, total fat explained an additional 2%, and waist circumference was not related. There is also a negative relationship between the amount of free leptin and both waist circumference and WHR (Magni et al., 2005). Thus, gluteofemoral fat deposits could influ-

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TABLE 1. Significant results of logistic regression for occurrence of menarche in 693 nulligravidas aged 10–14

| Variable | Wald statistic | Partial R | P | Odds ratio (CI) |
|--------------------------|----------------|-----------|---------|------------------|
| Hip circumference (cm) | 27.68 | 0.20 | <0.0001 | 1.22 (1.17–1.26) |
| Height (cm) | 14.05 | 0.14 | 0.0002 | 1.09 (1.06–1.11) |
| Age (years) | 11.43 | 0.12 | 0.0007 | 1.55 (1.36–1.76) |
| Triceps skinfold (mm) | 7.92 | –0.10 | 0.0049 | 0.91 (0.88–0.94) |
| Waist circumference (cm) | 6.62 | –0.09 | 0.0101 | 0.93 (0.90–0.96) |

Variables rejected as nonsignificant: biiliac breadth, race/ethnicity, weight, total fat, arm and thigh circumferences, suprailiac, subscapular, and thigh skinfolds.

ence the timing of menarche through their effects on blood leptin levels.

The purpose of this study is to explore whether the timing of menarche is more closely related to fat distribution or to skeletal growth and whether fat distribution is related to leptin levels. Because of the effects of lower-body vs. upper-body fat on leptin production, we predict that the likelihood of menarche will be positively related to hip circumference and negatively related to waist circumference, and that age at menarche will show the opposite associations. We also predict that blood leptin levels will be much more strongly related to hip than waist circumference in young women.

METHODS

To test these hypotheses in a multivariate context, we examined cross-sectional anthropometric data from the third National Health and Nutrition Examination Survey (NHANES III) collected from 1988 to 1994. The sample includes 38% non-Hispanic whites, 29% non-Hispanic blacks, 28% Hispanics, and 5% others. From a total of 1,165 females ages 10–14, we selected for forward-conditional logistic regression analysis those without menarche ($n = 573$, mean age 11.07 ± 1.03) and those whose self-reported age in years when menstrual cycles began and age at the time of examination were the same ($n = 120$, mean age 11.88 ± 1.00). Measures used for multivariate analysis included race/ethnicity, height, weight, total fat, hip, thigh, waist, and arm circumferences, subscapular, suprailiac, thigh, and triceps skinfolds, and biiliac breadth (National Center for Health Statistics, 1988). In addition, for purposes of within-sample comparison, we defined a low-fat subsample, selecting from the same 120 postmenarcheal girls those with less than 8 kg of total estimated fat ($n = 17$). These were contrasted with two comparison groups: 52 premenarcheal girls with comparable fat (<10 kg), age (>11), and height (>145 cm), and the remaining 103 postmenarcheal girls with fat levels of 8+ kg (age 12.00 ± 1.19 , fat 17.4 ± 7.2 kg).

We also examined the relationship between fat distribution and leptin levels in women with completed growth aged 20–29 in the NHANES sample. (The NHANES III did not measure leptin in women under 20 years of age.) The relation of fat to age at menarche was determined in 1,761 women with a mean age of 24.45 ± 2.86 and self-reported recalled age at first menses of 12.69 ± 1.66 . Fasting serum leptin levels were available for 758 of these women, with a mean age of 24.47 ± 2.87 , age at menarche of 12.65 ± 1.72 , and mean leptin level of 15.13 ± 10.95 fg/L. Leptin was determined by radioimmunoassay using a polyclonal antibody to recombinant purified human leptin.

Cross-sectional thigh fat area was determined from the thigh circumference and skinfold thickness, and

thigh fat volume, by multiplying fat area by femoral length; body fat was estimated from the triceps and subscapular skinfolds using the method of Slaughter et al. (1988) which has a standard error of 3.9%. Effect sizes were calculated using the method of Cohen (1992), and statistical analyses were performed using SPSS.

RESULTS

Comparing the 573 girls without menarche to the 120 examined in the year they reached menarche, the most significant predictor of menarche is hip circumference (Table 1). A 1-cm increase in hip size is associated with 22% higher odds of menarche, while a 1-mm increase in triceps skinfold is associated with 9% lower odds of menarche and a 1-cm increase in waist circumference, with 7% lower odds. Biiliac breadth is not a significant predictor if forced into the logistic regression model ($P = 0.94$). Total estimated fat, BMI, and weight are also not significant predictors of menarche in this model or in a model with age, height, and biiliac breadth ($0.19 < P < 0.82$).

Women who reach menarche despite low overall levels of body fat are an informative group. Only 17% of those aged 10–14 with less than 8 kg of total fat reported having had menarche compared with 66% of those with 8 kg or more. Compared with those of similar age, height, and fat levels without menarche (Table 2), the low-fat menarche group had significantly larger hip circumference, thicker thigh skinfold, lower WHR, and 15% larger mean thigh fat area with an additional 523 cc³ in combined thigh fat volume. Thus, those attaining menarche despite low overall body fat had proportionately more fat in gluteofemoral depots and less fat in the upper body compared with those who have not yet had menarche (Fig. 1). They also had a much lower WHR than those with menarche and higher fat levels (0.788 ± 0.022 vs. 0.832 ± 0.053 , $d = 1.16$, $P < 0.0001$).

In women 20–29, age at menarche is related to fat distribution in a similar way. In a stepwise regression with hip and waist circumference, height, total fat, age, and race/ethnicity, age at menarche is negatively related to hip circumference ($B = -0.030$, $P < 0.0001$) and positively to waist circumference ($B = +0.011$, $P = 0.044$) and height ($B = +0.032$, $P < 0.0001$). If thigh circumference is used in place of hip circumference, its effect is similar ($B = -0.054$, $P < 0.0001$). If hip circumference and biiliac width are entered with age and race/ethnicity, hip circumference is negatively related to age at menarche ($B = -0.023$, $P < 0.0001$) and biiliac width is positively related ($B = +0.037$, $P = 0.026$).

In the subsample of 758 women 20–29 with leptin measurements, as predicted, the effect of hip circumference on leptin levels is more than twice as great as that of waist circumference. Controlling for age, race/ethnicity, and height, a 1 cm increase in hip circumference increases leptin by 0.51 fg/L, while a 1 cm increase in

TABLE II. Comparison of young women with low fat levels and comparable age and height with menarche in past year or without menarche

| Variable | With menarche | | No menarche | | Effect size |
|-------------------------------------|---------------|--------|-------------|--------|-------------|
| | N = 17 | SD | N = 52 | SD | |
| Age (years) | 12.00 | 1.00 | 12.40 | 0.63 | -0.49 |
| Height (cm) | 154.85 | 5.84 | 154.98 | 5.65 | -0.02 |
| Estimated fat (kg) | 6.63 | 1.15 | 6.64 | 1.64 | -0.01 |
| Arm circumference (cm) | 21.01 | 1.49 | 21.49 | 1.56 | -0.31 |
| Triceps skinfold (mm) | 9.46 | 1.96 | 9.60 | 2.28 | -0.07 |
| Subscapular skinfold (mm) | 7.41 | 1.29 | 7.58 | 1.93 | -0.11 |
| Suprailiac skinfold (mm) | 7.33 | 1.62 | 8.36 | 3.77 | -0.38 |
| Hip circumference (cm) | 78.87 | 3.87 | 76.98 | 4.3 | 0.46* |
| Thigh circumference (cm) | 40.72 | 3.2 | 40.14 | 2.27 | 0.21 |
| Thigh skinfold (mm) | 14.7 | 4.3 | 12.55 | 3.32 | 0.56* |
| Thigh fat area (cm ²) | 52.99 | 16.03 | 45.20 | 12.10 | 0.55* |
| Thigh fat volume (cm ³) | 2004.71 | 656.59 | 1726.67 | 492.23 | 0.48* |
| Waist circumference (cm) | 62.09 | 2.98 | 62.47 | 4.24 | -0.11 |
| Waist-hip ratio | 0.788 | 0.022 | 0.813 | 0.049 | -0.68** |

* $P < 0.05$.

** $P < 0.01$.

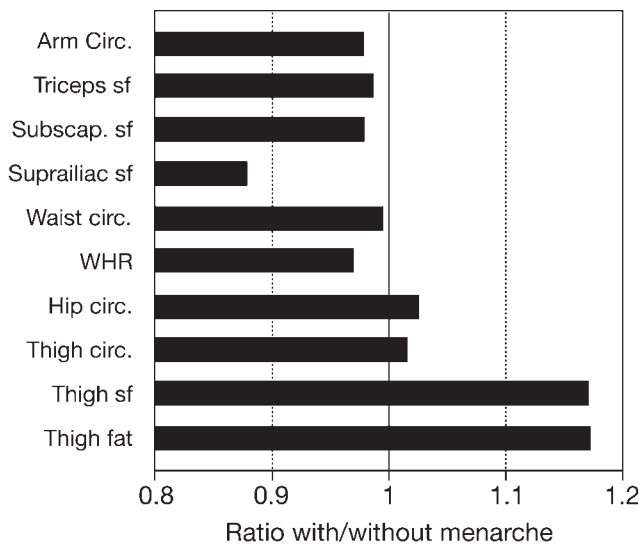


Fig. 1. Ratio of anthropometric measures in low fat young women with and without menarche.

waist circumference increases leptin by only 0.21 fg/L. Controlling for total fat as well, waist circumference is no longer related to leptin levels ($P = 0.86$) while hip circumference continues to be positively related ($B = 0.20$, $P = 0.002$). When biiliac breadth is entered with hip and waist circumference, it is negatively related to leptin ($B = -0.23$, $P = 0.035$). If hip and thigh circumferences are both entered, the coefficient for waist circumference is negative.

DISCUSSION

We found that the odds of menarche increase with increasing amounts of fat in the hips and buttocks, and decrease with increasing waist circumference and triceps skinfolds and that hip circumference is a more important factor than height or biiliac breadth. Young women with menarche despite having less than 8 kg of body fat have substantially more gluteofemoral fat when compared with a matched sample with low total body fat who have not yet had menarche. The low-fat menarche group also

have much lower WHR's than those with recent menarche and higher levels of total fat, suggesting that once a requisite amount of gluteofemoral fat has been stored, proportionately more fat is stored in the upper-body depots.

Thus, while the total estimated amount of body fat and weight are not significant predictors of menarche when added to skeletal growth, the distribution of body fat, as indicated by the relative amounts of upper-body and lower-body fat, is significantly related to menarche, especially in young women who reach this reproductive landmark with unusually low levels of total body fat. This suggests that body fat distribution may influence the timing of menarche although, alternatively, there may be a pubertal mechanism that increases lower-body fat deposition concurrent with or after menarche.

Because the data used in this study are cross-sectional, the relationship between fat distribution and the odds of menarche should be interpreted with caution. Since we have replicated the finding from longitudinal studies that total fat and weight are not significantly related to the timing of menarche when combined in multivariate analyses with measures of skeletal growth, our finding that, under the same multivariate conditions, age at menarche is more strongly related to fat distribution than to skeletal growth suggests that fat distribution may be a more important factor. Nevertheless, investigation of these relationships in a longitudinal context would be desirable.

In women 20–29, age at menarche is negatively related to hip and thigh circumference and positively related to waist circumference, stature, and biiliac breadth, again suggesting that fat distribution may influence the timing of menarche, though it is also possible that the age at menarche influences subsequent fat distribution. Since hip circumference is negatively related and biiliac width is positively related, this indicates that the relationship of hip circumference to age at menarche is not mediated by pelvic size, but rather by the portion of hip circumference external to the bony pelvis.

Also in women 20–29, each cm of hip circumference elevates leptin levels more than twice as much as equivalent increases in waist circumference. Moreover, when total fat is controlled, only hip circumference is significantly related to leptin. These findings are consistent

with other studies which indicate that gluteofemoral fat produces more leptin than upper-body fat.

As discussed above, leptin stimulates the pulse generator for GnRH in the hypothalamus. Leptin is also a direct stimulus for skeletal growth, acting directly on the growth plate (Maor et al., 2002), and age at menarche is inversely related to leptin levels (Matkovic et al., 1997). Higher leptin levels also preserve menstrual function in women with low fat due to anorexia nervosa (Miller et al., 2004). Thus, if young women with relatively more gluteofemoral fat produce more total and free leptin, this may increase GnRH pulse frequency and the likelihood of menarche. This effect would be especially conspicuous when overall levels of fat are low, as in our subsample with less than 8 kg of total fat.

Why might selection have built a menarche-timing mechanism sensitive to fat distribution? There is evidence that during fetal and infant brain development, maternal gluteofemoral fat is the main source of the long-chain polyunsaturated fatty acids (LCPUFA's) arachidonic and docosahexaenoic acid which comprise about 20% of the dry weight of the brain and play a key role in neurodevelopment (Hornstra et al., 1995; Innis, 2004; Marszalek and Lodish, 2005; McCann and Ames, 2005). The ratio of gluteofemoral to upper-body fat is also positively correlated with levels of LCPUFA's in the blood (Decsi, 2000; Klein-Platat et al., 2005) and in fat (Seidell et al., 1991). These gluteofemoral depots are protected from use until late pregnancy and lactation and become relatively depleted with parity while remaining intact in nulliparous women (Lassek and Gaulin, 2006). This view is consistent with evidence that gluteofemoral fat differs from upper-body fat in metabolism, mobilization, utilization, and consequences for health (Lapidus et al., 1994; Lassek and Gaulin, 2006).

CONCLUSION

The timing of menarche is related to a higher proportion of lower-body fat and lower proportion of upper-body fat, rather than to overall body fat levels or biiliac breadth, and these stores may be signaled internally by higher levels of leptin production by gluteofemoral fat. We speculate that the adaptive reason for this pattern may lie in the role of gluteofemoral fat in providing neurodevelopmentally important resources.

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