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## Differences in Endocrine Parameters and Psychopathology in Girls with Premature Adrenarche versus On-time Adrenarche

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### Abstract

Girls with premature adrenarche (PA) are at risk for multiple problems related to exaggerated androgen synthesis. Whether PA carries a risk of psychopathology remains unknown. This study examined group differences in: (a) anthropometric and endocrine parameters, and (b) mood and behavior problems, in 6-8 year-old girls with PA (n = 40) compared to on-time adrenarche girls (n = 36). PA girls were taller (p = 0.05) and heavier (p = 0.01) than the on-time adrenarche girls but body mass index showed no difference. PA girls had significantly (p < 0.05) higher adrenal androgen and testosterone concentrations but not cortisol or leptin. PA girls also had significantly more oppositional defiant disorder, and higher symptom counts reflecting anxiety, mood or disruptive behavior disorders. PA girls may be more vulnerable to psychopathology than on-time adrenarche girls. The challenge of future studies is to determine which PA girls are at risk for psychopathology and which are more resilient.

### Keywords

behavior problems; anxiety; puberty; adrenarche; adrenal androgens; testosterone; leptin

### INTRODUCTION

Literature reporting that puberty begins earlier in girls than in previous cohorts<sup>1</sup> brought controversy to the field of pediatric endocrinology and primary care<sup>2-4</sup> calling into question the age at which early puberty should be clinically evaluated rather than defined as 'normal'. Medical pathology may be present in early maturing girls<sup>5</sup>.

One early maturing group representing potential pathology is girls with premature adrenarche (PA). PA is defined as the appearance of pubic hair in girls < 8 years<sup>6</sup>. PA children have high-for-age adrenal androgens<sup>7</sup>, body odor, and axillary and leg hair. At PA onset, there is no gonadal axis activation and thus no thelarche or menarche.

PA has been defined as a benign variation of normal. However, many girls with PA have exaggerated adrenal and ovarian androgen biosynthesis<sup>8,9</sup>, polycystic ovarian syndrome (PCOS) in their reproductive years<sup>10</sup>, and risk for metabolic syndrome. PCOS may be associated with infertility, hirsutism, obesity, and early appearance of cardiovascular risk factors<sup>11-14</sup>.

Girls with PA also may be at risk for psychosocial problems<sup>15</sup>. The purpose of this study was two-fold. The first purpose was to evaluate endocrine and anthropometric differences between girls with PA and on-time adrenarche. It was hypothesized that adrenal androgens, testosterone (T), cortisol, and leptin would be higher in girls with PA. Differences in T and leptin may result from variation in adiposity, whereas cortisol differences may be related to hypothalamic pituitary adrenal (HPA) dysfunction in vulnerable individuals during biological transitions<sup>16,17</sup>. The second purpose was to examine differences in mood and behavior problems in girls with PA compared to on-time girls.

It was hypothesized that depressive symptoms/anxiety and acting out behaviors would be more frequent in PA compared to on-time adrenarche girls. This study represents the largest cohort girls with PA carefully matched with girls with on-time adrenarche, evaluated for psychological parameters in conjunction with the endocrine milieu.

## PARTICIPANTS AND METHODS

### Study population

The study included 40 girls with PA and 36 with on-time adrenarche (Table 1). Eligibility criteria for PA included: female, age 6-8 years, benign PA documented by a pediatric endocrinologist, Tanner 1 breast, Tanner 2 or greater pubic hair and prepubertal estradiol concentrations, English speaking, IQ  $\geq 75$ , and no acute/chronic disorders or medication that could influence endocrine measures (e.g., steroids). Girls with on-time adrenarche were recruited from the community and matched to the PA group with regard to age ( $\pm 6$  months), race, gender, socioeconomic status (SES<sup>18</sup>), and body mass index (BMI) ( $\pm 20\%$ ). Eligibility criteria for the on-time girls were the same as the PA girls with the exception that they were Tanner 1 breast and pubic hair.

### Procedures

PA girls were recruited from pediatric endocrine clinics in Pittsburgh and Cincinnati and from letters distributed to community clinicians in both communities. On-time girls were recruited from both communities via advertisements, flyers and the like. The study was approved by all Institutional Review Boards. Parents provided informed consent and children provided assent.

Of the 76 participants, 34 were recruited from the Pittsburgh site (18 [52.9%] PA); 42 were recruited from the Cincinnati site (22 [52.4%] PA). There was no site difference in the distribution of PA/on-time participants ( $\chi^2$ ,  $p = 0.96$ ). Children from the Pittsburgh site were slightly younger ( $7.3 \pm 0.7$  years vs  $7.7 \pm 0.9$ ,  $p = 0.02$ ). No other site differences were found in grade in school, race/ethnicity, parental education, SES, Tanner stage, height, weight or BMI.

For each child; the visit began between 11.30 and 13.00 h to control for diurnal rhythms in hormones. Girls were fasting for 120 minutes prior to blood sampling to eliminate potential post-prandial increases in cortisol. Visits were conducted in a General Clinical Research Center (GCRC).

## Measures

**Anthropometric and pubertal measures**—*Height and weight* were measured three times (Harpenden wall-mounted stadiometer; Holtain Ltd., UK) and the ScaleTronix stand on scale (ScaleTronix, Carol Stream, IL), respectively. Three values were averaged.

*BMI* was computed [weight (kg)/height (m<sup>2</sup>)]. Girls were also categorized as normal weight, at risk for overweight (BMI >85<sup>th</sup> percentile – 95<sup>th</sup> percentile), or overweight (>95<sup>th</sup> percentile) based on CDC criteria.

Lean body mass was computed<sup>19</sup>.

*Pubertal stage* was determined by physical examination by trained clinicians<sup>20</sup>. Inter-rater agreement on 25% of the examinations across the study was 100% for breast and pubic hair ratings.

**Laboratory assays**—Blood samples were drawn three times at 20 minute intervals to capture the ultradian cortisol rhythm. Samples were centrifuged, separated and serum was frozen at –80°C until assayed. Samples were pooled (other than cortisol), pair-matched for assay, and analyzed in duplicate.

*DHEAS* was measured using solid phase radio-immunoassay (RIA) (DSL, Webster, TX). Inter- and intra-assay coefficients of variation (CVs) were 12% and 5% at a concentration of 20 µg/dl.

*Androstenedione* was measured by RIA (Coat-A-Count, DPC Los Angeles, CA). Inter- and intra-assay CVs were 8% and 4% at 125 ng/dl.

*Testosterone* was assayed using the Active® Testosterone RIA kit from Diagnostic Systems Laboratories, Inc. Minimum detection limit was 0.08 ng/ml. Intra-assay CV ranged between 9.6% and 7.8% at a concentration of 0.94 and 19.1 ng/ml. The inter-assay CV was 8.6% at 0.7 and 8.4% at 16.06 ng/ml.

*Cortisol* was assayed on the Nichols Advantage® Specialty System using chemiluminescence. Sensitivity was 0.8 µg/dl. The intra-assay CV ranged between 8.7% and 3.8% at 2.3 µg/dl and 28.9 µg/dl. The inter-assay CV ranged between 17.4% and 8.7% at 2.3 µg/dl and 28.9 µg/dl. For cortisol, area under the curve (AUC) and net response (NET) were calculated with samples at 0, 20, and 40 minutes<sup>21</sup>.

*Leptin* was determined using an enzyme-linked immunosorbent assay (DSL, Webster, TX). Inter-assay and intra-assay CVs were 9% and 2% at 10 ng/ml.

*Estradiol* was measured using an ultrasensitive RIA (DSL, Webster, TX). Sensitivity was 1.0 pg/ml based on the mean ± 2 SD of 17 replicates of the 0 pg/ml assay standard. Inter- and intra-assay CVs were <5% at 20 pg/ml.

## Mood and behavior problems

The Diagnostic Interview Schedule for Children (DISC)<sup>22</sup> is a structured computerized interview administered to the parent. It is designed to screen for childhood psychiatric diagnoses in the past year, past month, and lifetime, and is scored using computer algorithms. Additionally, symptom counts were obtained.

The *Child Behavior Checklist (CBCL)*<sup>23</sup> records parent perception of behavior problems. Scoring results in eight subscales as well as two broad-band scores (internalizing,

externalizing), and a total behavior problem score. The proportion of participants who fell above the borderline clinical cut-off point (60+) was calculated. T-scores (standardized scores, mean = 50, SD = 10) and the corresponding borderline clinical rates were calculated. Reliability coefficients ranged from  $\alpha = 0.43$ - $0.86$  (mean =  $0.69$ ).

The *Teacher Report Form*<sup>24</sup> is parallel to the CBCL. Reliability coefficients in this sample ranged from  $\alpha = 0.51$ - $0.96$  (mean =  $0.82$ ). The proportion of participants who fell above the borderline clinical cut-off point (60+) was calculated.

The *Children's Depression Inventory (CDI)*<sup>25</sup> is a 27-item self-report measure of depressive symptoms. The reliability coefficient (total score) in this sample was  $\alpha = 0.87$ .

The *State Trait Anxiety Inventory for Children*<sup>26</sup> is a self-report measure for children under age 12 years and includes 20 state and 20 trait anxiety items. Reliability coefficients for state and trait anxiety were  $\alpha = 0.85$  and  $\alpha = 0.83$ , respectively.

*Relational aggression* was measured using a 4-item self-report<sup>27</sup>. Relational aggression is thought to reflect aggression expressed by girls compared to more acting out behaviors exhibited in boys. The reliability coefficient was  $\alpha = 0.61$ .

### Statistical analyses

Group comparisons were conducted to ensure balance on the potential confounding variables. Since none of the baseline variables were significantly different between the two groups, no co-variables were considered. Primary study outcomes were Internalizing, Externalizing and Total CBCL t-scores, selected since a young population would be less likely to have clinical diagnoses. Study outcomes were compared between two groups using or Fisher's Exact method for categorical data, and Student's t-test or the Kruskal-Wallis test (KW) on continuous or ordinal data. Multivariate analysis of variance (MANOVA) was used to examine overall group differences. Since MANOVA takes into account correlations between multiple items for each measure, no adjustment for multiple comparisons was considered. The study has 80% power to declare statistical significance (2-sided alpha = 0.05) for an effect size of 0.65 or larger using two groups t-test; while only 65% power is estimated for the study to detect a medium effect size of 0.5.

## RESULTS

### Group differences in anthropometric and hormone measures

Significant group differences were noted for height ( $p = 0.02$ ) and weight ( $p = 0.02$ ) with girls with PA being taller and heavier than on-time girls. BMI was not higher in PA compared to on-time girls ( $p = 0.09$ ). More PA girls were overweight and had significantly higher lean body mass ( $p = 0.004$ ) than on-time girls (Table 2).

For breast stage, all girls were Stage 1. For pubic hair, 23 PA girls were Stage 2 and 17 PA girls were Tanner 3. On-time girls had Tanner stage 1 pubic hair.

**Adrenal androgens**—PA girls had higher DHEAS ( $p = 0.0003$ ) and androstenedione ( $p < 0.0001$ ) than on-time girls.

**Testosterone**—A lower proportion of PA girls were under the detection limit of the assay (23.1 % in PA vs 56.3% in on-time adrenarche girls;  $p = 0.004$ ). PA girls had higher, T ( $p = 0.002$ ).

**Cortisol**—No differences were noted for cortisol indices.

**Leptin**—PA girls had higher concentrations of leptin than on-time girls ( $p = 0.02$ ). The difference became non-significant ( $p = 0.32$ ) after controlling for BMI. No correlation was found between leptin and BMI ( $r = 0.03$ ;  $p = 0.8$ ).

**Estradiol**—No group differences were noted. Two-group t-test comparisons found a group mean difference of  $0.70 \pm 1.59$  (effect size = 0.44,  $P = 0.07$ ).

#### Group differences in mood and behavior problems (Table 3 and 4)

**DISC diagnoses**—There were no group differences for diagnoses of anxiety or mood disorders. There was, however, a significantly higher rate for oppositional defiant disorder (ODD) in the past year (20% vs 3.1%;  $p = 0.04$ ), past month (17.5% vs 0%;  $p = 0.02$ ), and lifetime (20% vs 3.1%;  $p = 0.04$ ) in the PA compared to on-time girls.

**DISC symptoms**—Compared to on-time adrenarche girls, girls with PA had higher symptom scores by KW test for separation anxiety ( $p = 0.01$ ), specific phobia ( $p = 0.001$ ), generalized anxiety disorder ( $p = 0.01$ ), panic disorder ( $p = 0.01$ ), obsessive compulsive disorder ( $p = 0.01$ ), major depressive disorder ( $p = 0.001$ ), attention deficit/hyperactivity symptoms ( $p = 0.01$ ), hyperactivity ( $p < 0.001$ ), and ODD ( $p = 0.02$ ).

**CBCL**—PA girls had higher scores than on-time adrenarche girls for Social Problems ( $p = 0.03$ ), Anxious/Depressed ( $p = 0.03$ ), Aggressive Behavior ( $p = 0.02$ ), as well as the broad band scores for Externalizing Behavior ( $p = 0.01$ ), Internalizing Behavior ( $p = 0.01$ ), and Total Behavior problems ( $p = 0.05$ ). The proportion of girls falling above the borderline clinical cut-point of 60 was calculated and compared using Fisher's exact test. For all subscales, there was a higher rate of PA participants that fell at 60 or above, while statistical significance was found only for Social Problems (25% vs 6.25%,  $p = 0.05$ ) and Aggressive Behavior (17.5% vs 0%,  $p = 0.0123$ ). Similarly, consistently higher rates were found for PA girls for Externalizing Behavior (12.5% vs 6.3%,  $p = 0.45$ ) and Internalizing Behavior (20% vs 6.3%,  $p = 0.17$ ), although significance was reached only for Total Behavior problems (22.5% vs 3.0%,  $p = 0.02$ ).

**TRF**—Group differences were noted for Aggressive Behavior ( $p = 0.03$ ). Teachers of PA girls reported higher scores than did teachers of on-time girls. Although not significant, effect sizes were moderate for the difference in Social Problems (0.49,  $p = 0.07$ ) and Externalizing Behavior Problems (0.47,  $p = 0.08$ ). For all subscales except somatic complaints, there was a consistently higher rate of PA girls at 60 or above, while statistical significance was found only for aggressive behavior (27.3% vs 3.7%,  $p = 0.02$ ). For broad band scores, only Externalizing Behaviors was significantly higher in the PA group (24.2% vs 3.7%,  $p = 0.03$ ).

**CDI**—No group differences were noted ( $p = 0.13$ ), although the direction of means shows that PA girls report higher depression scores, albeit not significant.

**State Trait Anxiety Inventory**—There were no significant group differences in state ( $p = 0.27$ ) or trait ( $p = 0.69$ ) anxiety.

**Relational Aggression**—No group differences were noted in relational aggression ( $p = 0.84$ ).

## DISCUSSION

This study represents the largest cohort of girls with PA in which psychological problems were examined in conjunction with the endocrine milieu. Additionally, a carefully matched comparison group was included.

### Anthropometric and endocrine differences

Group differences in anthropometric indices support findings from previous studies reporting girls with PA are taller<sup>28</sup> and heavier<sup>29</sup> although not all studies agree<sup>11</sup>. For endocrine parameters, girls with PA had higher adrenal androgens than on-time girls. However, adrenal androgens can also be elevated in obesity<sup>30</sup>, and more PA girls were overweight. Girls with PA also had higher total testosterone. This difference may result from metabolism of adrenal androgens to T. Most earlier studies have not examined testosterone, with one exception in which higher free T was reported in girls with PA<sup>11</sup>. In that study, girls were older (10.04 years) and could have been in gonadarche. Obese peripubertal girls had higher T compared to non-obese girls, particularly at earlier stages of puberty<sup>31</sup>. Our sample had a greater frequency of overweight girls, perhaps contributing to higher T.

Similar to the findings of L'Allemand *et al.*<sup>32</sup>, leptin was not significantly higher in girls with PA when controlled for BMI. Leptin was higher in a smaller group of PA girls; some had already reached gonadarche<sup>33</sup>. The role of leptin in adrenarche remains unclear<sup>34</sup>. Leptin is necessary but not sufficient for initiation of puberty. Leptin also stimulates synthesis of adrenal androgens through enzymes essential for adrenal androgen production<sup>30</sup>. Thus, elevated leptin in PA may contribute to higher adrenal androgens.

No significant group differences were noted in cortisol indices, differing from an earlier study<sup>15</sup> and our current hypothesis. Regulation of the corticotroph may be no different in PA compared to on-time girls. Alternatively, venipuncture may not have provided a strong enough stimulus to the HPA axis.

### Differences in mood and behavioral problems

As hypothesized, girls with PA had significantly more diagnoses and/or symptoms of mood and behavior problems than on-time girls. More girls with PA than on-time girls met diagnostic criteria for ODD and had higher symptom scores for anxiety and disruptive behavior disorders. Although the majority of girls do not meet diagnostic criteria in all arenas or reach clinical cut-off scores, higher scores indicate problems that may interfere with parent-child interaction, peer relationships and school performance. Individual differences in behavioral phenotype warrant vigilance by health care providers and parents.

Biological transitions represent a period of vulnerability for negative psychological outcomes<sup>16,17</sup>. Higher concentrations of adrenal androgens were related to behavior problems and mood in healthy adolescents<sup>35-37</sup> and earlier puberty in adolescent girls has been related to various negative outcomes<sup>38-41</sup>.

Differences in mood and behavior problems in girls with PA may result from several potential reasons. First, such problems may result from organizational effects of hormones: programming *in utero* for behavior or function to be altered or expressed later in development<sup>42</sup>. Programming effects have been noted where HPA axis dys-regulation, along with hypertension and glucose intolerance, were evident in later life<sup>43,44</sup>. Further, programming effects on later psychopathology may occur with prenatal exposure to glucocorticoids<sup>45</sup>. Higher stress and its ensuing rise in glucocorticoids may interrupt development of the brain and HPA axis and, in turn, alter behavior. Second, hormones also may have activational effects<sup>46</sup>: that is, when hormones naturally rise, as in adrenarche, a

function or behavior may be influenced. These influences may be transitory in nature<sup>47</sup>. In PA, adrenal androgens are higher than age-matched peers and target tissues may be more sensitive to adrenal androgens. Hormones may contribute to mood and behavior problems, since steroid hormones can also act as neurosteroids<sup>48,49</sup> on the brain. Even though adrenal androgens are less potent than gonadal androgens, adrenal androgens have been associated with problem behaviors in healthy adolescents<sup>50-52</sup>. No other studies were found examining girls with PA and psychopathology.

Third, influences of early timing of puberty in PA on brain maturation have not been explored. For example, does brain maturation occur earlier in PA, or does early endocrine exposure hamper brain development? Brain changes occur prior to puberty, some result from puberty, while still others are independent of puberty<sup>47,53-56</sup>. Finally, mood and behavior problems may be more evident in girls with PA based on the 'maturational deviance' hypothesis<sup>57-59</sup> that proposes that more stress and adjustment problems are evident when pubertal development is early or late. Having a different appearance from same aged peers may be a chronic stressor resulting in sad affect or acting-out behaviors. Alternatively, the 'early maturation' or 'early timing' hypothesis emphasizes that early puberty is a disadvantage, as children miss the opportunity to accomplish normal tasks of mid-childhood<sup>57,59</sup>. With early developers, there is a mismatch in which society views them as mature by physical advancement, yet the socio-emotional arenas remain immature.

### Limitations

Defining PA as the cause of psychopathology cannot be accomplished from cross-sectional studies. Additionally, the majority of girls with PA in this study represent referrals from endocrine clinics. Thus, findings cannot be generalized to all girls with P A. Finally, the psychological findings may be different for boys with PA.

### CONCLUSIONS

In American culture, early timing of puberty is viewed more as the norm rather than the exception. However, not all early puberty comes without potential risk. Negative physical health outcomes may result from PA, a disorder once regarded as benign. This study provides further evidence that psychosocial problems can be associated with PA consistent with biological transitions being periods of risk for physical and emotional disorders in vulnerable individuals<sup>16,17</sup>. However, not all girls with PA had psychopathology. The challenge of future studies is to determine which girls with PA are at risk for problems and which are resilient. Until those studies are conducted, health providers should be vigilant in considering mood and behavioral disturbances in girls with PA.

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### REFERENCES

1. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. Secondary sex characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics*. 1997; 99:505–512. [PubMed: 9093289]
2. Emans SJ, Biro F. Secondary sexual characteristics and menses in young girls. *Pediatrics*. 1998; 101:949–950. [PubMed: 9599126]

3. Reiter EO. Have the onset and tempo of puberty changed? *Arch Pediatr Adolesc Med.* 2001; 155:988–989. [PubMed: 11529797]
4. Rosenfield RL, Bachrach LK, Chemaussek SD, Gertner JM, Gottschalk M, Hardin DS, Pescovitz OH, Saenger P. Current age of onset of puberty. *Pediatrics.* 2000; 106:622–623. [PubMed: 11012339]
5. Midyett LK, Moore WV, Jacobson JD. Are pubertal changes in girls before age 8 benign? *Pediatrics.* 2003; 111:47–51. [PubMed: 12509553]
6. Siegel SF, Finegold DN, Urban MD, McVie R, Lee PA. Premature pubarche: etiological heterogeneity. *J Clin Endocrinol Metab.* 1992; 72:239–247. [PubMed: 1309831]
7. Saenger P, DiMartino-Nardi J. Premature adrenarche. *J Endocrinol Invest.* 2001; 24:724–733. [PubMed: 11716159]
8. Ibanez L, Potau N, Zampolli M, Street ME, Carrascosa A. Girls diagnosed with premature pubarche show an exaggerated ovarian androgen synthesis from the early stages of puberty: evidence from gonadotropin-releasing hormone antagonist testing. *Fertil Steril.* 1997; 67:849–855. [PubMed: 9130889]
9. Ibanez L, Ong K, de Zegher F, Marcos MV, del Rio L, Dunger D. Fat distribution in non-obese girls with and without precocious pubarche: central adiposity related to insulinaemia and androgenaemia from prepuberty to postmenarche. *Clin Endocrinol.* 2003; 58:372–379.
10. Ibanez L, DiMartino-Nardi J, Potau N, Saenger P. Premature adrenarche—normal variant or forerunner of adult disease? *Endocr Rev.* 2000; 21:671–696. [PubMed: 11133068]
11. Andiran N, Yordam N, Kirazli S. Global fibrinolytic capacity is decreased in girls with premature adrenarche: a new pathological finding? *J Pediatr Endocrinol Metab.* 2005; 18:1373–1381. [PubMed: 16459463]
12. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev.* 1997; 18:774–800. [PubMed: 9408743]
13. Loucks TL, Talbott EO, McHugh KP, Keelan M, Berga SL, Guzick DS. Do poly cystic-appearing ovaries affect the risk of cardiovascular disease among women with polycystic ovary syndrome? *Fertil Steril.* 2000; 74:547–552. [PubMed: 10973653]
14. Talbott EO, Zborowskii JV, Boudreaux MY. Do women with polycystic ovary syndrome have an increased risk of cardiovascular disease? Review of the evidence. *Minerva Ginecologica.* 2004; 56:27–39. [PubMed: 14973408]
15. Dorn LD, Hitt S, Rotenstein D. Biopsychological and cognitive differences in children with premature vs. on-time adrenarche. *Arch Pediatr Adolesc Med.* 1999; 153:137–146. [PubMed: 9988243]
16. Charmandari E, Kino T, Souvatzoglou E, Chrousos GP. Pediatric stress: hormonal mediators and human development. *Horm Res.* 2003; 59:161–179. [PubMed: 12649570]
17. Dorn LD, Chrousos GP. Neurobiology of stress: understanding regulation of affect during female biological transitions. *Sem Reprod Endocrinol.* 1997; 15:29–45.
18. Hollingshead, AB. Four-Factor Index of Social Status. Yale University Press; New Haven, CT: 1975.
19. James, WPT. Research on Obesity. HMSO; London: 1976.
20. Marshall WA, Tanner JM. Variations in panem of pubertal changes in girls. *Arch Dis Child.* 1969; 44:291–303. [PubMed: 5785179]
21. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuro endocrinology.* 2003; 28:916–931.
22. Schwab-Stone M, Fisher P, Piacentini J, Shaffer D, Davies M, Briggs M. The Diagnostic Interview Schedule for Children-Revised Version (DISC-R): II. Test-retest reliability. *J Am Acad Child Adolesc Psychiatry.* 1993; 32:651–657. [PubMed: 8496129]
23. Achenbach, TM. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. University of Vermont; Burlington, VT: 1991.
24. Achenbach, TM. Manual for the Teacher's Report Form and 1991 Profile. University of Vermont Department of Psychiatry; Burlington, VT: 1991.



25. Kovacs, M. Children's Depression Inventory (CDI) Manual. Multi-Health Systems, Inc.; North Tonawanda, NY: 1992.
26. Spielberger, CD.; Edwards, CD.; Lushene, RE.; Montuori, J.; Platzek, D. STAIC Preliminary Manual. Consulting Psychologists Press; Palo Alto, CA: 1973.
27. Crick NC. Relational and overt aggression in preschool. *Dev Psychol.* 1997; 33:579–588. [PubMed: 9232373]
28. Voutilainen R, Perheentupa J, Apter D. Benign premature adrenarche: clinical features and serum steroid levels. *Acta Paediatr.* 1983; 72:707–711.
29. Guven A, Cinaz P, Bideci A. Is premature adrenarche a risk factor for atherogenesis? *Pediatr Int.* 2005; 47:20–25. [PubMed: 15693861]
30. Shalitin S, Phillip M. Role of obesity and leptin in the pubertal process and pubertal growth—a review. *Int J Obes Relat Metab Disord.* 2003; 27:869–874. [PubMed: 12861226]
31. McCartney CR, Prendergast KA, Chhabra S, Eagleson CA, Yoo R, Chang RJ, Foster CM, Marshall JC. The association of obesity and hyperandrogenemia during the pubertal transition in girls: obesity as a potential factor in the genesis of postpubertal hyperandrogenism. *J Clin Endocrinol Metab.* 2006; 91:1714–1722. [PubMed: 16492701]
32. L'Allemand D, Schmidt S, Rousson V, Brabant G, Gasser T, Grüters A. Associations between body mass, leptin, IGF-I and circulating adrenal androgens in children with obesity and premature adrenarche. *Eur J Endocrinol.* 2002; 146:537–543. [PubMed: 11916623]
33. Cizza G, Dorn LD, Lotsikas AJ, Sereika S, Rotenstein D, Chrousos GP. Circulating plasma leptin and IGF-1 levels in girls with premature adrenarche: potential implications of a preliminary study. *Horm Metab Res.* 2001; 33:158–143.
34. Apter D. The role of leptin in female adolescence. *Ann NY Acad Sci.* 2003; 997:64–76. [PubMed: 14644811]
35. Brooks-Gunn J, Warren MP. Biological and social contributions to negative affect in young adolescent girls. *Child Dev.* 1989; 60:40–55. [PubMed: 2702873]
36. Susman EJ, Nottelmann ED, Inoff-Germain G, Dorn LD. Hormonal influences on aspects of psychological development during adolescence. *J Adolesc Health.* 1987; 8:492–504.
37. Udry JR, Billy JOG, Morris NM, Groff TR, Raj MH. Serum androgenic hormones motivate sexual behavior in adolescent boys. *Fertil Steril.* 1985; 43:90–94. [PubMed: 4038388]
38. Ge X, Conger RD, Elder GH. Pubertal transition, stressful life events and the emergence of gender differences in adolescent depressive symptoms. *Dev Psychol.* 2001; 37:404–417. [PubMed: 11370915]
39. Graber JA, Seeley JR, Brooks-Gunn J, Lewinsohn PM. Is pubertal timing associated with psychopathology in young adulthood? *J Am Acad Child Adolesc Psychiatry.* 2004; 43:718–726. [PubMed: 15167088]
40. Hayward C, Killen JD, Wilson DM, Hammer LD, Litt IF, Kraemer HC, Haydel F, Varady A, Taylor CB. Psychiatric risk associated with early puberty in adolescent girls. *J Am Acad Child Adolesc Psychiatry.* 1997; 36:255–262. [PubMed: 9031579]
41. Michaud PA, Suris JC, Deppen A. Gender-related psychological and behavioural correlates of pubertal timing in a national sample of Swiss adolescents. *Mol Cell Endocrinol.* 2006; 25:254–255. 172–178.
42. Phoenix CH, Goy RW, Gerall AA, Young WC. Organizing action of prenatally administered testosterone propionate on the tissue mediating mating behavior in the female guinea pig. *Endocrinology.* 1959; 65:369–382. [PubMed: 14432658]
43. Nyirenda MJ, Lindsay RS, Kenyon CJ, Burchell A, Seckl JR. Glucocorticoid exposure in late gestation permanently programs rat hepatic phosphoenol pyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. *J Clin Invest.* 1998; 101:2174–2181. [PubMed: 9593773]
44. Weinstock M. Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? *Neurosci Biobehav Rev.* 1997; 21:1–10. [PubMed: 8994205]
45. Seckl JR, Meaney MJ Glucocorticoid programming. *Ann NY Acad Sci.* 2004; 1032:63–84. [PubMed: 15677396]

46. Arnold AP, Sreedlove SM. Organizational and activational effects of sex steroids on brain and behavior: a reanalysis. *Horm Behav.* 1985; 19:469–498. [PubMed: 3910535]
47. Sisk CL, Zehr JL. Pubertal hormones organize the adolescent brain and behavior. *Front Neuroendocrinol.* 2005; 26:163–174. [PubMed: 16309736]
48. Stoffel-Wagner B. Neurosteroid metabolism in the human brain. *Eur J Endocrinol.* 2001; 145:669–679. [PubMed: 11720889]
49. Walker EF, Sabuwalla Z, Huot R. Pubertal neuro-maturation, stress sensitivity, and psychopathology. *Dev Psychopathol.* 2004; 16:807–824. [PubMed: 15704816]
50. Nottelmann ED, Susman EJ, Inoff-Germain GE, Cutler GB Jr, Loriaux DL, Chrousos GP. Developmental processes in early adolescence: relations between adolescent adjustment problems and chronologic age, pubertal stage, and puberty-related hormone levels. *J Pediatr.* 1987; 110:473–480. [PubMed: 3819952]
51. Susman EJ, Inoff-Germain G, Nottelmann ED, Loriaux DL. Hormones, emotional dispositions, and aggressive attributes in young adolescents. *Child Dev.* 1987; 58:1114–1134. [PubMed: 3608660]
52. Susman EJ, Dorn LD, Chrousos GP. Negative affect and hormone levels in young adolescents: concurrent and predictive perspectives. *J Youth Adolesc.* 1991; 20:167–190.
53. Dahl RE, Spear LP. Special Issue: Adolescent Brain Development: Vulnerabilities and Opportunities. *Ann NY Acad Sci.* 2004; 1021:472.
54. Dahl RE. Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. *Ann NY Acad Sci.* 2004; 1021:1–22. [PubMed: 15251869]
55. Giedd J, Blumenthal J, Jeffries N, Rajapakse JC, Vaituzis AC, Liu H, Berry YC, Tobin M, Nelson J, Castellanos FX. Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. *Prog Neuropsychopharmacol Biol Psychiatry.* 1999; 23:571–588.
56. Sisk CL, Foster DL. The neural basis of puberty and adolescence. *Nat Neurosci.* 2004; 7:1040–1047. [PubMed: 15452575]
57. Brooks-Gunn J, Warren MP. Measuring physical status and timing in early adolescence: a developmental perspective. *J Youth Adolesc.* 1985; 14:163–189.
58. Caspi A, Moffitt T. Individual differences are accentuated during periods of social change: the sample case of girls at puberty. *J Pers Soc Psychol.* 1991; 61:157–168. [PubMed: 1890586]
59. Petersen, AC.; Taylor, B. The biological approach to adolescence: biological change and psychosocial adaptation. In: Adelson, J., editor. *Handbook of the Psychology of Adolescence.* Wiley; New York: 1980.

**TABLE I**

Descriptive statistics of demographic and anthropometric characteristics of girls with premature adrenarche (PA) and on-time adrenarche

	PA(n = 40)	On-time (n = 36)
<b>Age</b> (years)	7.7 ± 0.9	7.4 ± 0.8
<b>SES</b>	43.7 ± 13.1	47.1 ± 11.1
<b>Race</b>		
<b>Caucasian</b>	23 (57.5%)	26 (72.2%)
<b>African-American</b>	12 (30.0%)	7 (19.4%)
<b>Other</b>	3 (7.5%)	2 (5.6%)
<b>Biracial</b>	2 (5.0%)	1 (2.8%)
<b>Weight</b> (kg)	31.6 ± 9.0**	26.5 ± 6.0
<b>Height</b> (cm)	128.5 ± 6.8**	123.7 ± 7.0
<b>BMI</b>	19.0 ± 4.1	17.1 ± 2.7
<b>BMI category</b>		
<b>85<sup>th</sup> percentile - at risk for overweight</b>	19 (47.5%)	10 (27.8%)
<b>95<sup>th</sup> percentile - overweight</b>	14 (35.0%)*	5 (13.9%,)
<b>Lean body mass</b> (kg)	24.5 (5.0)**	21.4 (3.9)

Results are given as means ± SD, or number (percentage).

SES = socio-economic status based on Hollingshead scale<sup>18</sup>; BMI = body mass index [weight (kg)/height (m)<sup>2</sup>].

\* p 0.05

\*\* P 0.01.

**TABLE 2**

Descriptive statistics of hormone concentrations in girls with premature adrenarche (PA) and on-time adrenarche (mean  $\pm$  SO)

	PA(n=40)	On-time (n = 36)
<b>DHEAS</b> ( $\mu$ g/dl)	78.0 $\pm$ 61.2 <sup>***</sup>	30.6 $\pm$ 37.9
<b>Androstenedione</b> (ng/dl)	81.9 $\pm$ 36.8 <sup>***</sup>	42.8 $\pm$ 32.9
<b>Leptin</b> (ng/ml)	22.7 $\pm$ 28.8 <sup>*</sup>	12.4 $\pm$ 12.5
<b>Testosterone</b> (ng/ml)	0.20 $\pm$ 0.11 <sup>***</sup>	0.13 $\pm$ 0.09
<b>Cortisol mean</b> ( $\mu$ g/dl)	9.2 $\pm$ 4.1	9.1 $\pm$ 4.5
<b>Cortisol AUC</b> (min- $\mu$ g/dl)	380.8 $\pm$ 177.9	371.1 $\pm$ 192.8
<b>Cortisol NET</b> (min- $\mu$ g/dl)	61.2 $\pm$ 113.3	47.7 $\pm$ 128.8
<b>Estradiol</b> (pg/ml)	5.12 $\pm$ 1.7	4.43 $\pm$ 1.4

Cortisol: mean = mean of sample 0, 20, 40 min; AUC = area under the curve; NET = net response.

\* p <0.05

\*\* P 0.01

\*\*\* P 0.001.

**TABLE 3**

Descriptive statistics for psychological measures for girls with premature adrenarche (PA) and on-time adrenarche

	PA (n = 40)	On-time (n = 36)
<b>Children's Depression Inventory (total raw)</b>	8.7 ± 9.1	6.0 ± 4.5
<b>State anxiety (t-score)</b>	47.6 ± 10.2	49.7 ± 7.9
<b>Trait anxiety (t-score)</b>	48.1 ± 11.9	46.5 ± 12.8
<b>Relational aggression</b>	9.6 ± 3.8	9.4 ± 2.9
<b>TRF externalizing</b>	52.0 ± 10.1	47.9 ± 6.8
<b>TRF internalizing</b>	48.5 ± 10.8	47.0 ± 10.4
<b>Total score</b>	48.9 ± 12.6	46.7 ± 9.3
<b>DISC symptom count</b>		
<b>Agoraphobia</b>	0.18 ± 0.45	0.03 ± 0.18
<b>GAD</b>	3.08 ± 2.38 <sup>**</sup>	1.59 ± 1.74
<b>OCD</b>	0.48 ± 0.91 <sup>**</sup>	0.03 ± 0.18
<b>Panic</b>	0.31 ± 0.49	0.13 ± 0.71
<b>PTSD</b>	0.55 ± 1.29	0.34 ± 1.62
<b>Separation anxiety</b>	3.13 ± 2.43 <sup>*</sup>	1.77 ± 1.93
<b>Social phobia</b>	2.25 ± 3.67 <sup>*</sup>	0.72 ± 1.76
<b>Specific phobia</b>	1.40 ± 1.13 <sup>**</sup>	0.59 ± 0.54
<b>MDD</b>	4.93 ± 3.71 <sup>***</sup>	2.09 ± 1.91
<b>ADHD</b>	5.10 ± 4.87 <sup>*</sup>	2.59 ± 3.23
<b>CD</b>	1.43 ± 2.01	0.78 ± 1.10
<b>ODD</b>	6.45 ± 3.07 <sup>*</sup>	4.59 ± 3.10

\* p 0.05

\*\* P 0.01

\*\*\* P 0.001.

TRF = Teacher report form; DISC = Diagnostic Interview Schedule for Children; GAD = generalized anxiety disorder; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder; MOD = major depressive disorder; ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; ODD = oppositional defiant disorder.

**TABLE 4**

Descriptive statistics for the t-scores of the Child Behavior Checklist in girls with premature adrenarche (PA) and on-time adrenarche

	PA (n =40)	On-time (n = 36)	Effect size
<b>Subscales</b>			
<b>Withdrawn</b>	53.1 ± 5.6	52.1 ± 4.6	0.17
<b>Somatic complaints</b>	56.8 ± 7.2	54.1 ± 5.4	0.39
<b>Anxious/depressed</b>	54.2 ± 5.3*	51.8±3.4	0.51
<b>Social problems</b>	55.2 ± 7.3*	51.8±4.6	0.54
<b>Thought problems</b>	52.0 ± 4.8	50.7 ± 2.3	0.31
<b>Attention problems</b>	53.8 ± 5.8	52.2 ± 4.8	0.29
<b>Delinquent behavior</b>	53.7 ± 5.0	52.6 ± 5.7	0.25
<b>Aggressive behavior</b>	54.0 ± 5.4*	51.5 ± 3.2	0.64
<b>Broad band scores</b>			
<b>Internalizing</b>	50.7 ± 10.5*	46.1 ± 9.0	0.67
<b>Externalizing</b>	50.3 ± 9.0*	45.0 ± 8.7	0.45
<b>Total score</b>	50.0 ± 11.2**	41.5 ± 14.3	0.57

\*  
p 0.05

\*\*  
p 0.01.