Gender Differences at Puberty

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8 Puberty and depression

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In this chapter we will examine evidence concerning the emergence of an excess of unipolar depression in females during adolescence. We will also present new data from the Great Smoky Mountains Study (GSMS) in support of an approach that combines consideration of both the endocrinology of puberty and the effects of stress on depression.

The phenomenon to be explained


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Thus the question "Why does depression become more common in girls than boys during adolescence?" largely reduces to the question "Why does the prevalence of depression increase in girls during adolescence?" The remainder of this chapter will focus on the latter question.

It comes as no surprise that a substantial change in the prevalence of depression occurs during adolescence led to the suggestion that the changes of puberty might be some way be responsible. This idea has spawned many studies, but it is only recently that studies of sufficient size to disentangle a variety of pubertal and other effects have begun to clarify the situation. For instance, it was only with the appearance of larger general population-based studies that the timing (in terms of age) of the increased prevalence of depression ruled out the possibility that it might be related to adolescence (occurring around age 6-8 years), rather than puberty. However, puberty is a complex developmental process, and before turning to the evidence relating depression and puberty a brief diversion into the physiology of puberty is required (see also chapter 2).

Pulmonary and depression

Physiology of female puberty and its implications for the study of psychopathology

Changes in the hypothalamic-pituitary-gonadal (HPG) axis

Although the HPG and hypothalamic-pituitary-adrenal (HPA) axes show a brief burst of activity in the first months after birth (Shute, 1984), circulating concentrations of gonadotropins and gonad and adrenal steroids are very low in early- to mid-childhood. An increase in adrenal androgen output (adrenarche) occurs at around 6-8 years (DeVoef and Forest, 1976; Ducharme, et al., 1976; Kahnsky, et al., 1991; Parker, et al., 1976; Reuss, Pfaudler, and Reuss, 1977; Scortichini and Piantini, 1975). Adrenarche precedes the earliest changes of puberty on the HPG axis by about two years, and was initially thought to act as a trigger for its onset (Collo and Ducharme, 1975). It is now known that this is untrue (Counte, et al., 1987). When puberty begins in early to mid-adolescence. These changes, in turn drive increased gonadotropin (luteinizing hormones [LH] and follicle stimulating hormone [FSH]) pulse frequency and amplitude. Early puberty is marked by the appearance of frequent, closely spaced, entrained nighttime pulses of LH, beginning in late childhood (Dunkel, et al., 1990; Wu, et al., 1990). LHRH pulse frequency decreases in late puberty in females (although amplitude continues to increase in males) as its release becomes more sensitive to negative feedback control from gonadal steroids (Dunger, et al., 1991; Marshall, et al., 1991; Wenzinck, et al., 1986). An important sex difference established over the course of puberty is that females develop pulsatile gonadotropin releasing hormone (GnRH) secretion along with fluctuating estradiol and progesterone (Marshall, et al., 1991). Measurement of this pattern extends from before menarche to several months or years beyond in the course of establishing regular ovulation and luteal function (Vito and Azper, 1980; Wenzinck, et al., 1990).

Secondary sex characteristics and menarche

Puberty is a gradual event mediated through physiological mechanisms that are operative at ages 8-12 years, or one to three years prior to the
notion of morphological puberty (the growth spurt and appearance of secondary sexual characteristics) and well before micturition (Wennoak, et al., 1985; Wettz, et al., 1986; Wu, et al., 1990; see also chapter 2). In other words, the physiological changes of early puberty long predate the appearance of the features upon which most research on the relationship between puberty and psychopathology has been based. For instance, in one from data from the GSMS, there is a substantial linear relationship between FSH and age (Pearson r = .35, p < .001) in girls aged 9 and above in Tanner stage 4 (i.e., girls showing secondary sexual characteristics at all) that is not reflected in morphological status. Similarly, once Tanner stage 5 is reached, there is still continuing hormonal change, but again it is not reflected in body morphology, at least as measured by the Tanner scheme. Indeed, as girls begin to cycle, age and Tanner stage can have relatively subtle effect on levels of FSH, LH, and estrogen, because their levels become primarily controlled by the menstrual cycle. The key point here is that, at different stages of puberty, the correlations among the various manifestations of puberty change dramatically. This, in turn, means that the best marker for a given effect of puberty on psychopathology can be expected to change depending on the developmental stage covered in a particular study (see chapter 1). For instance, if an effect of puberty on depression was in reality caused by changes in androgen and estrogen levels, but direct hormonal measures are not available to a particular study, whether age, pubertal status, pubertal timing or some other "surface" marker of pubertal status appeared to have an effect on depression would depend in part on the distribution of developmental levels of participants in the study.

The implications of variations in end-organ sensitivity to sex steroids

Neuroendocrine changes are obviously greatly reflected in morphological signs of puberty, such as growth and the development of secondary sexual characteristics; for example, those rated by Tanner's pubertal stage (Apter, 1980; Barr, et al., 1980; Lee and Migeon, 1975; Lee, et al., 1975; Siroenken, et al., 1970; Siroenken and Passer, 1975). The causal cascade in morphological development commences from maturation of CNS-generated pulsatility of gonadotropin release that stimulates activity of the peripheral glands (glands and adenals) (Hayes and Credley, 1998; McGonigal, et al., 1998; O'dea and Ma, 1998; Phillips, et al., 1997; Woldhuis, 1996). Rising levels of gonads and adrenal steroid hormones, in turn, stimulate development of secondary sexual characteristics (see chapter 2). In girls, breast development is driven by rising estrogens, while the emergence of pubic and axillary hair is associated with increasing androgens. The primary source of estrogens is the ovary, while androgens are primarily produced in adrenals (with increasing contributions from the ovary, which begins to fluctuate as ovarian cyclicity becomes established). Hence, it has been argued that morphological development represents a biopsy for cumulative steroid exposure.

However, hormone levels explain on average less than half the variance in morphological pubertal development and growth in girls (Nottelmann, et al., 1987b). Sex characteristic development is modulated by end-organ sensitivity, which is controlled by the number and type of tissue receptors and other intracellular conditions (aromatisation and other steroid metabolic enzymes, trophic kinases and other secondary messengers) (Leyman, 1995). Furthermore, responses by these peripheral target tissues may be but a poor reflection of the central impact of steroid hormones at puberty. The discovery of two major classes of estrogen receptors, alpha and beta (Murphy, et al., 1997), with numerous variants in each receptor type (Lo, et al., 1998), has revealed new complexities in estrogen action. Mapping of ER distribution by density and subtype in the brain and periphery has demonstrated patterns of differential expression of both types across (and even within) brain regions (Lafuente, et al., 1998; Michler, Goetle, and Ben-Jonathan, 1998; Orentreich, et al., 1998), but also identified tissue-distinctive ER expression in peripheral target tissues such as the breast (Murphy, et al., 1997). The upshot of such findings is that we cannot expect steroid effects on brain tissue to be a very precise mirror of their impact in the CNS. Although libido is actually known about the mechanisms by which sex steroids might be related to developmental risk for psychopathology (reviewed in Serman, 1997; Young and Korszun, 1998; see also chapter 3), present evidence suggests that, in the absence of highly locale-specific probes for estrogen action in the CNS, circulating levels of steroids probably represent the best general measure of CNS steroid exposure.

There is no single "best measure" of puberty

Let it seem that we are arguing that hormonal measures will provide a "better" measure of puberty, let us be clear that this is not so. Puberty is a complex, multi-faceted phenomenon. There can be no single "best" measure of puberty (see chapter 1). Rather, we want to indicate the need to recognize that hormones, Tanner stage, and menarche (to name but three aspects) are all measures of correlated, but meaningfully different aspects. We have argued that circulating hormone levels are likely to be the
best available correlate of hormonal actions in the CNS. But we are also quite sure that self-report of breast development is a better measure of breast development than is circulating estrogen level. Different theories of the relationship between puberty and depression have concentrated attention on the potential effects of different aspects of puberty, and it seems likely that this has led to much confusion.

Potential pathways from puberty to depression

We have found it helpful to think of four basic types of pathways by which puberty might affect depression. Those are summarized in figure 8.1. The three least studied areas divide the potential causes of depression into three broad groups: CNS effects (both physiological and psychological), pre-puberal physiological manifestations of puberty (both hormonal and morphological), and extra-organismic (environmental, social, or otherwise). The pituitary sits at the interface between the two major intra-organismic compartments.

Pathway 1

The first and simplest pathway indicates changes in levels of inter-organismic risk factors in the transition of increased levels of depression. Simply put, more bad things happen to older girls, so they become depressed more often. Here puberty is simply a marker for the changing circumstances faced by adolescents as they age, and is not directly involved in the generation of depression at all. The other three pathways all depend upon effects of puberty directly.

Pathway 2

The second pathway implies pre-pubertal physiological changes contingent upon the morphological changes of puberty (such as breast development). The basic idea is that changed body morphology impacts upon girls' self-perceptions and/or the reactions of others to them, in such a way as to increase the risk for depression.

A number of studies of monochoric or morphological development (secondary sex characteristics; usually measured by Tanner stage; Tanner, 1962) have suggested that the timing of pubertal status may be significantly related to mood or other disturbances, as measured by a wide variety of scales (Angold and Rutter, 1992; Brooks-Gunn and Warren, 1989; Ge, Conger, and Elder, 1994; O'connor, et al., 1988; Pfeiffer, Brooks-Gunn, and Warren, 1991; Spivak, et al., 1987a; see also chapters 12 and 13). Early puberty has been associated with problem behaviors in girls, but with good adjustment in boys (see Stein and Magnusson, 1996) for a review; we also chapters 7, 12, and 13). Stein and Magnusson (1990) argued from their influential longitudinal study that the negative effects of early development in girls were generated by the impact of early maturation on girls' social lives, and their early introduction to sexual life, for which they might be cognitively unready. However, these effects had largely disappeared by the time the girls were in mid-adolescence, whereas the female excess of depressive disorders continues throughout adulthood.

Overall, the scale-based pubertal staging literature contains many failures to replicate findings from studies to study (Carrin and Caissa, 1994; Green and Ulman, 1982; Stein and Magnusson, 1990), and it is uncertain how much of this is because different studies have used different designs and different measures of psychopathology and puberty. However, it cannot be said, by any means, to have provided very solid support for the idea that early puberty is a major factor in the emergence of the female excess of depression.

Sex differences in pubertal timing and depressive diagnoses are few and far between. Howard and colleagues (1997) found that onset of internalizing
symptoms measured by various scales were associated with earlier puberty. However, the effects for depression scores alone was not significant. In a much smaller subset of girls followed into high school, they also reported a significant association (OR = 1.2) between earlier pubertal timing and the development of interview-based diagnoses of "internalizing disorders" (any depression, subclinical bulimia, social phobia, or the anxious type disorder). Graber and colleagues' study from the Oregon Adolescent Depression Project (Grabr et al., 1997) produced contradictory results. Self-report and interview measures (for adolescents were asked whether they thought they were early, on-time, or late) had higher lifetime rates of depression than on-time matures (30.2% vs. 22.1%), but late matures had the highest lifetime rates overall (33.8%). Both of these effects were statistically significant. On the other hand, rates of recent major depression were lowest in the early matures (2.5%), intermediate in the on-time group (3.5%), and highest in the late matures (3.0%). None of these differences was statistically significant.

Pathway 3

The third alternative implicates brain maturational changes occurring around the onset of puberty in both the initiation of puberty itself and in the alterations of mood regulation that exacerbate risk for depression at the CNS level (see chapter 3). These changes may then generate or exacerbate depressive mood changes and depressive cognitive styles. In other words, it suggests that changes indexed by gonadotropin secretion should be most closely linked to changes in rates of depression. As indicated in figure 8.1, such effects might be mediated by the tropic hormones themselves, or operate through quite separate mechanisms that correlate with tropic hormone status.

The previous evidence relating to these possible pathways has been unconvincing. In the NIMH study of puberty and psychopathology, FSH levels correlated with negative emotional tone in girls but not boys (Nestlerman et al., 1993; Sussman et al., 1987).

Pathway 4

Pathway four in figure 8.1 represents models that focus on the CNS effects of steroid hormones. Such models posit that the effects of puberty on depression are not dependent upon the effects of body morphology on self-image, social and sexual behavior, or changing levels of stress dependent upon them (or any other such thing), but instead are dependent upon the effects of peripherally synthesized steroid hormones on brain functioning (or structure, or both; see chapter 3). Previous evidence for the effects of sex steroids on depression has been suggestive, but far from definitive. The NIMH study of puberty and psychopathology (Nestlerman et al., 1987a; Nestlerman et al., 1987b; Sussman et al., 1987a; Sussman et al., 1987b) found negative associations between the testosterone:estradiol ratio, sex hormone binding globulin, and androstenedione concentration and negative emotional tone in boys. Researchers also reported an association of early maturation (measured by estradiol and testosterone:estradiol ratio) with reduced negative emotional tone in boys, but more negative emotional tone in girls. Beresin-Grann and Warren (1989) found that negative affect increased in 10- to 14-year-old girls during rapid estrogen rise. A one-year follow-up of 72 girls (Paikoff et al., 1991) found a significant linear relationship between estradiol level at time 1 and depression one year later according to one depression scale, but no such effect in relation to two other depressive scales.

None of these hormonal studies had sufficient power to test apart the possible contributions of age itself, the indirect psychosocial impacts of morphologic pubertal status, and the more direct impact of the different groups of hormones that change at puberty. In addition, all of them used depression scale scores only, rather than interview-based diagnoses.

It will be immediately apparent that these four pathways are not mutually exclusive, and that effects could operate at all of these levels. Our interest in the rest of this chapter is in trying to understand which of these possible pathways contributes to increasing rates of depression in girls in the Great Smoky Mountains Study (GSMS). We begin with a brief overview of the design of the GSMS.

An overview of the methods of the Great Smoky Mountains Study

A detailed account of the study design and instrumentation used can be found in earlier literature (Angold, Costello, and Worthman, 1999; Costello et al., 1996). Sampling frame

A representative sample of 4,500 children aged 9, 11, and 13, recruited through the Student Information Management System of the public school systems of eleven counties in western North Carolina, was selected using a household equal probability design. As close as possible
to the child's birthday, a screening questionnaire was administered to a parent (usually the mother), either by telephone or in person. This consisted of fifty-five questions from the Child Behavior Checklist about the child's behavior ("externalizing") problems, together with some basic demographic and service use questions. All children scoring above a predetermined cutoff score of 20 (designed to include about 25% of the population) on the behavioral questions, plus a 1 in 10 random sample of those scoring below the cutoff, were recruited for the longitudinal study. Eighty percent of eligible families agreed to participate in the interviews for at least one wave (1,073 of 1,346). A 100 percent oversample of American Indian children was also collected, but data from this sample are not included here.

Shortly after being screened, eligible children and one of their parents were interviewed. They were reinterviewed using a very similar assessment protocol at multiple follow-up waves, one, two, and three years later. Here we present data from the first three annual waves of data collection, because we only had funding to complete hormone assays on these waves. The sample considered here, therefore, consists of 465 girls aged 9-15 on whom we had a total of 1,983 interview observations from the first three waves of data collection.

Because sexual development is a sensitive topic, we showed the Tanner stage assessment to parents before giving it to the children, and specifically asked permission to use it. At each wave, between 2.6 percent and 7.3 percent of parents refused to have the scale administered to their female children. However, refusal to complete the Tanner stage assessment was not significantly related to depression scores or diagnoses, so it seems unlikely that this additional source of missing data was a source of bias in the results.

At each wave, between 22.8 percent and 24.8 percent of female participants refused to give blood for hormone measurements (separate consent for the finger prick procedure used here was sought). Again, there was no significant relationship between depression status and missing hormone data, so again it seems unlikely that the results will be substantially biased by missing data in this area. Number of girls with hormone data at each wave were: wave 1 N = 339; wave 2 N = 353; wave 3 N = 310.

Measures

Psychiatric symptoms and disorders

Children and parents were interviewed using the Child and Adolescent Psychiatric Assessment (CAPA; Angold, et al., 1995), which generates a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994). Diagnoses were generated from symptom endpoints by computer algorithms. If a parent or child reported a symptom as present in the past three months, it was counted toward the relevant CAPA/DSM-IV scale score or diagnosis. This three-month "primary period" was selected rather than, say, a one-year or lifetime period, because shorter recall periods are associated with more accurate recall (see, e.g., Angold, et al., 1996). We considered three depression diagnoses: DSM-IV major depressive episode, dysthymia, and depression not otherwise specified (NOS). The last of these diagnostic categories comprised individuals who met the DSM-IV experimental criteria for Minor Depressive Disorder (American Psychiatric Association, 1994, p. 719).

The CAPA also contains a section covering the occurrence during the last three months of thirty-eight life events (Costello, et al., 1998). Apart from a simple count of the number of such events that occurred, three subscales counted lost (N = 11), violence-related (N = 13), and social network related (N = 9) events.

Pubertal morphologic scores

Self-drawings of pubertal morphologic status based on the standard Tanner staging system (Tanner, 1962) were performed with the aid of schematic drawings of secondary sexual characteristics (breasts and pubic hair). Each rating correlated well with physical examination based on Tanner stages (Dorn, et al., 1990; Duke, Litt, and Gross, 1980; Frankoewski, et al., 1987; Morris and Udry, 1980; Schlesinger, Turner, and Juvins, 1992). Each child was provided with ten appropriate schematic drawings and requested to rate herself on each dimension. Both self-ratings were averaged to yield a single individual score (ranging from 1 = prepubertal, to 5 = an adult level of development).

Blood spot collection and hormonal assays

Hormone samples were obtained at the beginning of the interview session, as follows: two finger-prick samples were collected at 20-minute intervals, applied to specially prepared paper, immediately refrigerated upon drying, and express-shipped (without refrigeration) to the laboratory within two weeks of collection. Samples were then stored at -23 degrees C until they were assayed.

Blood spot FSH and LH were measured using modifications of commercially available fluoroenzymometric kits for assay of these hormones.
Analytic strategy

The presence of repeated measures and screen-stratified sampling required the use of weighted analyses to generate unbiased population parameter estimates and to avoid "sandwich" type variance corrections (Duggin, Liang, and Zeger, 1994; Pickles, Dunn, and Vanpraet-Bergen, 1995) to produce appropriate confidence intervals and p values. These were obtained using generalized estimating equations (GEE) in SAS PROC GENMOD.

A summary of previous findings

Our first foray into this area (Anzold, Conzel, and Worhnan, 1998) involved analyses of age, pubertal timing, and Tanner stage on the probability of depression in both boys and girls over the first four annual waves of the OSMS (we could use four waves because the hormone data, available only for three waves, were not involved). To make a long story short, we found that Tanner stage provided a better fit for the prediction of depression than did age, and that once Tanner stage was controlled, there was no significant effect of age on depression diagnoses (while the effect of Tanner stage was significant). There was no effect of depression of the timing of puberty, whether measured by age of onset of menarche, or achievement of particular Tanner stages. These findings suggested that some aspect of puberty itself was related to increasing prevalence of depression, and that pubertal stage was not just a marker for nonpubertal age-related factors. However, it appeared that it was achieving a particular developmental level that was important, not the age at which that level was achieved. At this point, a version of pathway 2 involving pubertal sta-
tus (but not timing) effects was still viable, but could not be differentiated from possible effects through pathways 3 and 4.

We then went on to examine a variety of HPG axis hormonal effects on depression in girls alone (Anzold, Costello, and Worhnan, 1999). We focused on girls because only they had Tanner-stage-dependent increases in depression. The results here were striking. Both T and E2 levels had strong independent effects on depression, but even more notable was the fact that T and E2 accounted for all of the effects of Tanner stage (the OR for Tanner stage fell from 3.4 to 1.0 when these hormones were included). There were also indications that the effects of T on depression were nonlinear — being manifested only above a certain threshold. We shall return to the threshold issue later. For now, we simply note that explanations in terms of pathway 2 are not compatible with these findings. We also measured levels of PSH and LH and found that they had no ef-
fect on depression rates over and above those accounted for by T and E2.

There was, therefore, no support for pathway 3. This leaves pathway 4 as the sole recipient of support among the explanations involving pu-

berty directly. However, it was still possible that increased levels of stress in adolescence might be responsible for part of the increase. Indeed, it changes in stress were more strongly correlated with steroid hormone levels than either age or Tanner stage, then the whole apparent effect of T and E2 could be the result of confounding. This latter scenario seems rather implausible, but it is at least a theoretical possibility.
Our next aim is to test the predictions of pathway I using life events as a marker for stress. As a prelude to that, however, we first return to the question of the existence of a sex steroid threshold in the prediction of depression.

**Sex steroid threshold**

At the intracellular level, these apparent effects of both testosterone and estradiol could represent only an estrogenic effect, since when behavioral effects of testosterone in animals have been investigated at the level of the brain structures involved, most have proved to occur via estrogen receptors following intracellular aromatization of testosterone to estrogen (Braunstein, et al., 1990; Ramsenau, et al., 1990). Since estrogen is the latest of the hormones studied here to begin to rise in puberty, an intracellular estrogen effect could first appear as an effect of peripheral testosterone and only later manifest directly as an effect of peripheral estrogen. In our analyses so far, we have treated T and E2 separately. This adds complexity to explanatory statistical models, and if both were acting at the same receptors in their effects on depression, then the combined level of T and E2 would actually be a more physiologically appropriate index of pubertal status for our purposes.

We therefore developed a combined sex steroid level (SSL) by simply summing the measured molarities of T and E2 (an appropriate combinatorial approach because one molecule of T is aromatized to one molecule of E2). We then divided the distribution of SSLs into deciles, and plotted the prevalences of depression in those deciles (figure 8.2). This plot shows even more pronounced threshold effects than did that for T alone. The curve appears to have three regions. First there is a flat portion with very low levels of depression corresponding to SSLs up to 1.3 nanomolar. The second region with rates of depression about five times as high is generated by SSLs between 1.3 nanomolar and 2.3 nanomolar. The final region involving a further quadrupling of the rate of depression is associated with SSL levels above 2.3 nanomolar. We divided the observations into SSL groups based on these three cut points. The differences between these groups were all significant (1 vs. 2: OR = 4.6, 95% CI 1.4 - 13.59, p < .01; 2 vs. 3: OR = 8.41, 95% CI 1.3 - 53.4, p < .05; 1 vs. 3: OR = 20.32, 95% CI 7.0 - 57.9, p < .0001).

Since the effect of E2 considered alone had appeared to be linear in our previous analyses, we then fit a model to the depression data that included SSL reduced to the triad to be just described, and added E2 as an additional predictor. E2 had no significant residual effect on the probability of depression (OR = 1.01, p = .10). There was similarly no residual effect of T (OR = 1.01, p = .6).

**Figure 8.2 Relationship between sex steroid level and depression**

The prevalence of life events in mature and immature girls

There is no doubt that a variety of family and environmental acute and chronic stressors and problems are associated with depression (and a variety of other problems) in children and adolescents (see, e.g., Compa, Great, and Wu, 1994; Gooden and Altham, 1991; Gooden, Wright, and
of a "power problem," because we know we had sufficient power to find a difference in rates of depression between mature and immature girls with high statistical confidence. If a substantial cause of depression were to have been changing rates of life events, then we must have had good power to detect it. So at this point, pathway 1 has failed the test, along with pathways 2 and 3. Pathway 4, on the other hand, has received substantial support.

The effects of life events in mature and immature girls

It is all very well to say that pathway 4 is supported by our data, but what does that mean? At this point it means that we have established a strong connection between SSL and a black box that we have conveniently labeled "neurochemical mechanisms involved in depression." It is completely unclear what those mechanisms are, or how they relate to other risk factors for depression. It is obviously not the case that having an SSL above 1.3 nanomolar is "the cause of depression." If it were, then all psychologically normal women of reproductive age would be depressed all the time. The enormous literature on psychosocial predictors of depression in adults shows, without a shadow of doubt, that other factors need to be taken into account. The question, then, is: "What are the mechanisms by which higher levels of sex steroids lead to increased rates of depression?"

One possibility is that there is an increase in mature girls' "sensitivity" to the depressive effects of negative life experiences (see chapter 3). This implies the presence of an interaction between life events and SSL, such that life events have relatively little impact in the immature and a larger impact in the mature girls. To examine this possibility, we fitted a series of logistic regression models with depression as the outcome and numbers of life events (total, network, loss, violence), SSL status, and the interaction of life events and SSL status as the predictors. The results are shown in table 8.1. In every case, the OR for the effect of life events was smaller in the more mature girls. However, none of the interaction terms was significant, so we may conclude that there were no significant differences in the effects of life events on depression between the more and less mature girls. In other words, the more mature girls were not more sensitive to the depressive effects of life events than the less mature girls. Our results, therefore, agree with those of Goodyer and colleagues (1990), who reported that paternal status made no difference to the effects of life events on depression and anxiety in a comparison of clinic cases and normal controls.
Table 8.1. The effects of life events on the probability of being depressed in immature and mature girls (logistic regression results)

<table>
<thead>
<tr>
<th>Type of life event</th>
<th>Immature OR (95% CI)</th>
<th>Mature OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.8 (1.4-2.2)</td>
<td>1.4 (1.1-1.7)</td>
</tr>
<tr>
<td>Violence</td>
<td>2.4 (1.9-3.0)</td>
<td>2.6 (2.4-2.9)</td>
</tr>
<tr>
<td>Divorce</td>
<td>2.0 (1.5-2.6)</td>
<td>1.8 (1.5-2.2)</td>
</tr>
<tr>
<td>Separation</td>
<td>2.7 (2.2-3.5)</td>
<td>1.7 (1.5-2.0)</td>
</tr>
</tbody>
</table>

Conclusions
In this study, our findings point towards sex steroids having an effect on adolescent girls' likelihood of becoming depressed, that is, independent of body morphology, the timing of pubertal changes, or stress levels. We want to emphasize again that this does not mean that we believe stress is not an important component in the etiology of depression. We have seen that in both immature and more mature girls recent life events have very substantial effects on the probability of depression. The point is that the effects of pubertal hormonal status cannot be explained either by changes in levels of life events or by changing sensitivity to the depressiveogenic effects of life events. Of course, it remains possible that changing rates of estrogen specific types of stressors (perhaps family relationship difficulties or negative parenting styles) might explain these effects, but our work suggests, at the very least, that the effects of puberty on depression cannot be explained by any general change in susceptibility to stressors. Explanations in terms of changing levels of stress also fail to provide any parsimonious account of our findings. In order to "explain" the pubertal effects, a stressor would have to be substantially more closely confined with total sex steroid level than with secondary sex characteristics. We can think of no likely mechanisms by which such a situation might arise. On the other hand, we know that estrogen has effects on CNS amnergic systems, so pathway 4 in figure 8.1 is physiologically plausible, as well as being supported by our data.

However, we do not know how changes in the central mechanisms related to depression are impacted by changes in peripheral sex steroids. We are currently pursuing further analyses that we hope will shed light on that key question.

References
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