0021-972X/96/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 81, No. 10
Printed in U.S.A.

EXTENSIVE PERSONAL EXPERIENCE

Delayed Puberty*

HOWARD E. KULIN

Chief, Division of Pediatric Endocrinology, Department of Pediatrics, The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033

Patients with delayed puberty are frequent referrals to family practitioners, pediatricians, and endocrinologists. The problem, of course, is almost always not just a delay in the appearance or progression of secondary sexual characteristics, but also of stature. In fact, a large proportion of short stature referrals are boys in the peri-pubertal age group who sense their difference from peers both in height and in sexual maturity. While the majority of patients are boys, female referrals are still common, and gonadal dysgenesis variants must be assiduously pursued.

The clinical approach to these children has become increasingly complex as the diagnosis and treatment of short stature patients has evolved over the past few years. Unfortunately, the success of our diagnostic armamentaria has been disappointing in many cases, based on arbitrary cut-off points for dynamic growth hormone testing or integrated hormone concentrations. Additionally confounding is a physiological slow down in the growth rate of many boys just before the pubertal spurt.

To add to the dilemma, many time-honored, diagnostic categories have been threatened. We realize, increasingly, that many patients who are not growing well may have multifactorial origins, including intrauterine cause, a familial/genetic base, constitutional elements, nutritional origins, or behavioral components. Idiopathic short stature, surprisingly, is recent terminology, expressing diagnostic frustration and limitations in detecting partial growth hormone deficiency or defective growth hormone action, or other unclear causation.

Into this mix enter many patients with pubertal delay as assessed by our relatively firm knowledge of the appearance and progression of physical changes in the second decade of life. The diagnostic approach to and the biological origins of such individuals have been well described in textbooks and journal articles. The paradigms of hypo- and hypergonadotropic hypogonadism are clearly defined and still serve the clinician well. There is usually little diagnostic confusion about the hypergonadotropic patient of adolescent age; by early in the second decade of life, elevated levels of FSH and LH can be detected with ease. Hypogonadotropism in this age group is another question, however, and will be addressed as the major focus of this article.

While referral patients and parents certainly are seeking reassurance about the fundamental normality of the mechanism of sexual maturation, pubertal delay (and the usually attendant short stature) is a psychosocial problem. Admittedly, hormone deficiency may be permanent and may also reflect more dangerous disease (central nervous system tumor must always be ruled out); but such origins are rare considering the numerous (male) patients who seek counsel. Upon presentation it is also important to ascertain who is actually bothered most about the situation–child, parent, or physician. It is additionally useful to define whether diminished stature, diminished secondary sexual characteristics, or both are the major complaints. Clearly, the combination of statural diminution and sexual infantilism is a sizeable burden indeed for any young teenager–boy or girl. No studies, to my knowledge, have tried to discern the relative negative contributions of stature *vs.* pubertal development. It is my impression that a good deal of statural limitation can be sustained by patients who have some degree of sexual maturity. That statement is not to discount the trauma of reduced adult height in our society, but for children of pubertal age, their concern is how the outside world categorizes them with respect to peers. Herein the problem compounds even further as, again, little or no data bear on the quandary of how we age/stage categorize an individual in routine social circumstances.

The primary thesis of this article is to emphasize an active interventional stance in the use of exogenous sex steroids in the management of patients who present with delayed puberty. This interventional message is given by one who has been a (relative) therapeutic nihilist throughout his professional career. I have dragged my feet frequently in the use of growth hormone in short patients with possible partial somatotropin deficiency; I have delayed the use of GnRH superagonist use in many of my patients who present with possible sexual precocity. The reasons for my activist view regarding the trial treatment of patients with pubertal delay will become clearer below.

Diagnostic approach to the patient with pubertal delay

The importance of history, physical examination (*e.g.* olfaction), and a multitude of potential laboratory studies

Received March 11, 1996. Revision received May 2, 1996. Accepted May 9, 1996.

Address all correspondence to: Professor Howard E. Kulin, Chief, Division of Pediatric Endocrinology, The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center, 500 University Drive, P.O. Box 850, Hershey, Pennsylvania 17033.

* References for this article are listed alphabetically and direct the reader to general reading. The listed references are not specifically cited in the text.

should not be minimized in the evaluation of pubertal delay. For the sake of the current discussion, however, the most pressing question is the nature of gonadotropin function. More importantly, the key diagnostic query is not whether puberty has begun or will begin, but whether the process will progress. To me, many endocrinologists have confused these issues and have assumed that a given stage of pubertal advance provides a reasonably secure likelihood of continuation; that supposition is generally true because a variation of normal puberty–so-called constitutional delay–is common, and hormone deficiency is rare. Nonetheless, the degree of hormone deficiency covers a wide spectrum and is seldom complete. Furthermore, in the partial gonadotropin deficiency setting, pubertal onset may be timely and only progression of sexual maturation incomplete.

Normal physiology brings attention to the long duration of the pubertal gonadotropin rise. The initiation of the process, in fact, probably goes back to mid- or late-childhood, certainly to age seven or eight. Increasing data indicate that a major increment in gonadotropin levels actually occurs well before the appearance of secondary sex characteristics, the time-honored physical signal that reproductive maturity has begun. Thus, the total time interval for gonadotropin change during human puberty may span a decade and, perhaps, even longer given the normal extremes of this event. The importance of detecting physical change is not to be minimized, but the predictive value of such monitoring may be limited. Compared to the undefined neural events that initiate puberty and consequent gonadotropin increments, breast development and increasing testicular size are late events; rising sex steroid levels may not be detected until rather advanced stages in the whole maturational process. Even for a given stage of pubertal development very large inter-individual variations in pituitary and gonadal secretions exist.

Figure 1 delineates the patterns of change that may arise in the evolution of gonadotropin deficiency. There is only sparse information bearing on these presumed trends because the required longitudinal data have been lacking. Most likely, the classic pattern in patients with constitutional delay is a late onset of FSH/LH increments, a rise that parallels the norm, and the attainment of adult levels at a later age than normal. Because these changes take place over several years and the slope of the rise even in the norm (and constitutional group) is very variable, it is presumptuous to assume that hormone data from a single time point will be very reassuring. Current practice, however, has tended to utilize the results from single time point measurements of gonadotropins or sex steroids, or the responses to dynamic stimuli (*e.g.* GnRH) as diagnostic and, therefore, predictive of complete sexual maturity.

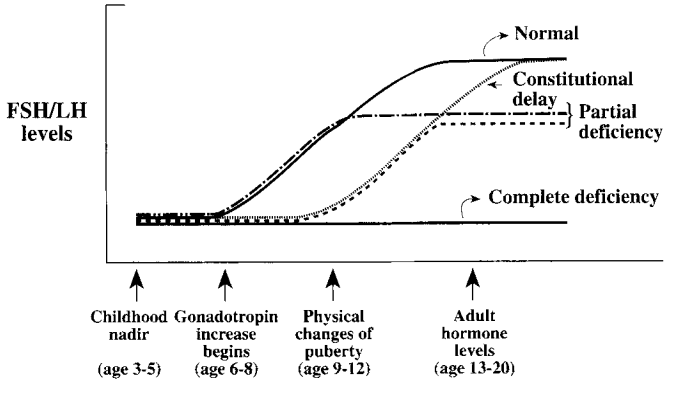

FIG. 1. Patterns of FSH/LH production associated with pubertal delay and hypogonadotropism. The normal age-related changes noted along the X-axis are approximations. Partial gonadotropin deficiency may result in either a late onset or incomplete progression of the expected gonadotropin increments.

In the patient with a bone age advance greater than 12–13, the diagnosis of complete gonadotropin deficiency is relatively easy to make (Fig. 1). More perplexing diagnostically are the FSH and LH trends in intermediate categories of hypogonadotropic hypogonadism, illustrated in Fig. 1 as partial deficiency. Results from such patients may display a late onset, progressive increase, and low adult levels of FSH and/or LH, or, alternatively, an individual may initiate the pubertal hormone process on a timely basis but not attain adult levels of function. These later presentations represent incomplete development, perhaps typified in milder forms by the "fertile eunuch" syndrome. These variants of gonadotropin deficiency also meld into patients with true extremes of pubertal delay, individuals who may or may not have a delayed onset of puberty but who do not arrive at apparent adult maturity until their early twenties. Some of these latter patients may have mild growth hormone deficiency as well and may display some compromise in stature on that basis. Thus, because of the long and variable trajectory of the gonadotropin rise during childhood and adolescence, caution should be brought to diagnostic measurements made at one time point in this process.

The specific gonadotropin testing techniques also warrant comment. The advent of monoclonal antibodies, sandwich-type assays, and fluorometric detection methodologies have increased the sensitivity of gonadotropin measurement by over 50-fold. Consequently, the reliability of data that assesses circhoral and circadian secretory modes has surely been improved by such methodologies. But pulsatile secretion requires multiple blood samplings over several hours to gain a clear idea of basal hormone levels. Ironically, the increase in assay specificity provided by the new technology may increase the variability of results encountered with different kit reagents.

The mainstay of gonadotropin testing has traditionally involved the use of GnRH stimulation. From a diagnostic point of view the GnRH test has been required to amplify the floor of the rather insensitive radioimmunoassay. Whether the existence of more sensitive assays will obviate such stimulatory testing remains to be seen. More recently, the long-acting gonadotropin releasing hormone analogue has been utilized to assess sex steroid production following stimulation, but the above caveats still hold. Whether GnRH testing is employed or not, these procedues involve the need for multiple serum samples from any single point in time evaluation.

My own approach to measuring gonadotropins in children has been the use of short-term, timed urine samples. Concentrating the specimen has additionally improved sensitivity, there is a high correlation with clinical states, and there

is great simplicity in attaining repeated samples. These advantages allow sequential measurements to be made with ease as the aforementioned gonadotropin trajectory is followed. Recent studies have used unextracted urine with the more sensitive assays, further simplifying the methodology.

Even with sensitive, specific, and sequential gonadotropin measurements, diagnostic quandaries remain. We have actually found that measurements made over a 2-yr period may not provide an accurate diagnosis of partial FSH and/or LH deficiency in a considerable number of patients. If urine gonadotropins triple over a 2-yr time period, there is a 95% chance of normality, but not certainty. When then should we discharge such individuals from our surveillance?

For the female, regular menses is the logical endpoint. For the male, a testosterone level at the lower limit of the adult male range (*e.g.* 250 ng/dL or 8.7 nmol/L) seems reasonable. Some patients require follow-up into the late teens or early twenties to rule out very mild hormone deficiencies by these means. While the classically described rise in testosterone is very steep, the major portion of the increment occurring over a year or less, some constitutionally delayed boys may evolve a much more prolonged pattern of change (see below). I believe adult-sized testes are not a sufficient end point since the bulk of gonadal constituents are of germinal cell origins.

For many referrals, repeated physical examinations, sequential endocrine testing, and reassurance provide adequate management. A significant number of patients remain, however, who may not receive the message of reassurance so happily. More importantly, 2 years of follow-up is far too long a period for an impatient teenager, striving at all junctures to emulate peers. In these individuals, interval treatment becomes a pressing need while biding time.

Short-term sex steroid treatment in the management of pubertal delay

The more inclusive goals in treating patients with pubertal delay should consider not only the presumed behavioral gains (requiring somatic changes) but also bone calcium and the possible induction of endogenous pubertal processes. The preceding section stressed the fact that sequential follow-up over years may be required for correct diagnosis. It is over this long time frame, during an important developmental period of life, that behavioral issues may arise.

The psychological effects ascribed to pubertal delay are very varied and can include depression, oppositional behavior, psychosomatic complaints, low self-esteem, poor school performance, reduced peer contact, aggression toward peers, immature goals for age, and general social immaturity. Whether any of these possible outcomes relate directly to sex steroid effects on the brain remains unknown but of great interest. Alternatively, a change in appearance–encompassing height, secondary sexual characteristics, and identification by peers and adults–may be required for a smooth adolescent transition. As already mentioned, which of these perceptual arenas is paramount for a given child (*e.g.* stature *vs.* breast development) is unknown. The few existent studies relating sex steroids and behavior are almost exclusively correlational, relating a given behavior to a given trend in endogenous hormone levels.

Preliminary data from our own current investigation on how sex steroids influence adolescent behavior do suggest that estrogen administration (to girls) and androgen administration (to boys) may directly effect the outcome of performance on specific aggression inventories. The unique study protocol employed, comparing results during sex steroid treatment periods to placebo periods, allows conclusions regarding hormone causation to be based on an interventional design rather than correlational analysis. Furthermore, the aggression score changes obtained in both sexes suggest that the androgen-induced effects in the male may actually require the endogenous conversion of testosterone to estrogen, akin to recently postulated mechanisms for the growth-promoting effects of androgens. But how hormones impact on adolescent behavior really remains a remarkably understudied arena, despite the treatment decisions we base on presumed behavioral considerations.

The realization that peak bone mass occurs toward the end of the second decade of life and is sex-steroid dependent provides another strong impetus for normalizing the androgenic or estrogenic milieu during the teenage period. What has not been defined is exactly how narrow the window of opportunity for such treatment is and whether there is a threshold for the timing and amount of sex steroid on calcium accretion. Nonetheless, there are data suggesting that a delay of treatment into the twenties in hypogonadal males may not allow optimal bone density to be achieved, and bone densities in young adult patients with a history of constitutional delay are reduced. These considerations, along with the behavioral ones, provide important reasons to generate an increase in levels of circulating sex steroid to the adolescent clearly lacking such hormone effects.

An additional reason for the early use of sex hormone treatment in the management of pubertal delay is the hypothetical induction or hastening of normal pubertal processes. The basis for such expectations is most visibly seen in the evolution of secondary central precocity in untreated (or undertreated) patients with congenital adrenal hyperplasia. Following concomitant and early advances in bone age in such individuals, hypothalamic maturity is attained with attendant increases in gonadotropin production.

We have recently administered intermittent sex steroids for three 3-month periods (in increasing dosage) over 18 months to a group of boys with constitutional delay without finding any clear evidence for such an effect. Preliminary data from ten subjects, shown in Fig. 2, suggest that such a treatment regimen does not appear to uniformly influence the endogenous time clock, even with an associated advance in secondary sex characteristics to late pubertal stages. Surprisingly, a rather sluggish rise in endogenous testosterone occurred in six of these boys (with older bone ages), as indicated in the upper right panel of Fig. 2. One boy, in fact, did not display any endogenous testosterone increases until after completion of the 18-month protocol. Other workers have reported that short-term oral androgens have not caused the pulsatile secretory mode to advance to more mature levels in constitutionally delayed boys. Thus, no data to date have argued convincingly that one can effectively activate the pubertal timing mechanisms with exogenous treatment regimens that do not unduly accelerate bone age.

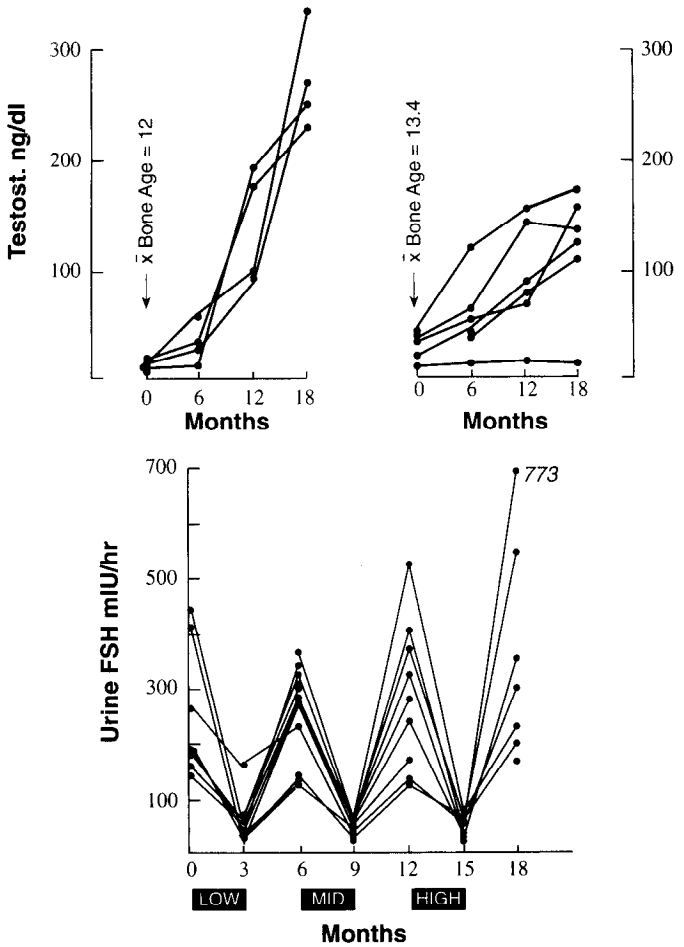

FIG. 2. Results from ten boys with constitutional delay in puberty who were followed for 18 months or more during a treatment protocol that entailed testosterone enanthate injections at 25 mg (LOW), 50 mg (MID), and 100 mg (HIGH) every 2 weeks for 3 months at each dose level. Placebo treatment was given to each patient in the alternate 3-month periods (*i.e.* 3–6, 9–12, and 15–18 months), causing expected rises in urine FSH levels after suppression during treatment (*lower panel*). Testosterone results obtained before starting the protocol and then following placebo in four boys (*upper left panel*) showed a prompt and rapid rise toward the adult male range, akin to published data in the normal male adolescent; testosterone treatment may or may not have influenced such trends. However, in six boys whose post-placebo results are shown in the *upper right panel* no hastening of endogenous testosterone production by the exogenous regimen was evident; rather, sluggish changes occurred, and one patient exhibited no testosterone increments within the 18-month study period. All ten subjects eventually achieved testosterone measurements of more than 230 ng/dL (8.0 nmol/L).

We are left, then, with an uncertain situation in the management paradigms of delayed puberty and hypogonadotropism. Diagnostic certainty is low, even with follow-up over a few years, and the exact (somatic or hormonal) requirements for fostering normal behavior are poorly understood. The most popular management choice is observation and reassurance in the most numerous group of patients who present with presumed constitutional delay. On the other hand, the absence of side effects and relative ease of administration of exogenous sex steroids warrants strong consideration for short-term trial therapy in these adolescents. Based on clinical experience alone I have increasingly become an advocate of this later direction.

Many different regimens have been utilized in trial treatments to male patients with delayed puberty. Although GnRH has been given on a long-term basis and can induce adult hormone levels, pump administration is neither practical nor generally acceptable to the adolescent. Human CG has also been employed for many years as a means of stimulating endogenous androgens in the male. The relatively frequent injections are a disadvantage, and hCG is very expensive.

Exogenous testosterone preparations are the mainstay in treating the adolescent boy who requires virilization. By modifying the testosterone molecule (most commonly ethyl or methyl substitutions in the 17- position), oral therapy is possible but liver function abnormalities may appear rarely. The anabolic steroid oxandrolone is an example and represents a compound employed widely over many years in the treatment of patients with delayed puberty. While height acceleration will occur, changes in secondary sexual characteristics are usually limited, consistent with the weak androgenic potency of the steroid.

Esterification of the 17-α-hydroxyl group of testosterone is another modification of the steroid nucleus and provides a slow release, lipid soluble, depot formation. One such drug, testosterone undecanoate, is absorbed by intestinal lymphatics and can also be ingested orally (usually 2–3 times a day). A new sublingual preparation, testosterone cyclodextrin, may prove useful in the pubertal setting but requires 3 times a day administration. Experience with transdermal steroid preparations remains very limited in the male or female patient of pubertal age.

The testosterone esters must be given parenterally, and the intermediate acting cypionate or enanthate are usually injected at intervals of 2–4 weeks. These preparations are my personal choices for the replacement of androgens in a boy of pubertal age. There is a large literature bearing on the safety and effectiveness of these substances in adolescent boys, and no evidence exists for growth compromise when proper dose and duration are chosen. Most studies have limited treatment periods to less than a year, but at low doses longer exposure intervals have been used safely. Progression of secondary sex characteristics and hormone levels after cessation of a therapy course is most reassuring.

In an ongoing (unpublished) study of 40 boys with delayed puberty, 24 of whom had constitutional delay, we have employed a somewhat longer treatment protocol than usual. The regimen (see Fig. 2, *lower panel*) uses 25 mg testosterone enanthate given every 2 weeks for 3 months and then a similar period off treatment; 50 mg of the drug is then administered with similar injection frequency for another 3 months, and a further 3-month observation period ensues; a final 3 months of treatment employs 100 mg given every 2 weeks with a third off-treatment period to follow. Over the 18-month interval, height is increased, secondary sexual characteristics become late pubertal, and undue bone age advance has not been observed. It is my impression that patients and parents are accepting and grateful for such intervention. I have used a similar protocol in adolescent-aged females, employing oral Premarin (Wyeth-Ayerst, Phil-

adelphia) in 3-monthly intermittent sequences at 0.15 mg, 0.3 mg, and 0.6 mg daily. Breakthrough bleeding has not occurred in girls so treated, who are then moved on to combined oral contraceptive therapy if permanent hypogonadism is present.

The use of human growth hormone in the treatment of patients with constitutional delay in growth and adolescence remains controversial. A physiological drop in growth hormone production can occur with the slow down in growth velocity that appears just before the pubertal growth spurt in some boys. While exogenous somatotropin can increase height velocity in some patients during this period, final adult stature is probably not significantly influenced by such intervention. Similarly, there is no evidence that growth hormone will hasten the onset of puberty in individuals with constitutionally delayed growth.

A small subgroup of patients who may warrant growth hormone testing and who may exhibit laboratory results that suggest mild somatotropin deficiency are perplexing management problems. These individuals are particularly short, growing slowly, and may exhibit borderline chemical evidence of hyposomatotropism. Some of these patients may warrant a growth hormone trial with or without sex steroids pending extensive patient/parental choice and very individualized selection. A significant increase in linear growth, without an undue advance in bone age, is reassuring evidence against growth hormone deficiency in those individuals who are treated only with sex steroids. Most of these patients will also normalize their growth hormone responses to provocative testing after estrogen or testosterone exposure.

Summary and conclusions

Despite a great increase in sophistication regarding dynamic testing and hormone assays, the diagnosis of hormone deficiency, sex steroid or somatotropin, remains difficult in many patients presenting with short stature and delayed puberty. I feel the incidence of mild sex hormone deficiencies is frequent enough (perhaps 10% of all male referrals for adolescent delay) that attention to diagnosis must extend over the duration of the pubertal process, at least for 2 yr in most patients and, in some individuals, considerably longer.

While many adolescents handle their pubertal delay well, an unclear number do not. The exact origin and nature of their psychological trauma remains poorly defined. Nonetheless, these individuals appear to benefit by interventional treatment with sex steroids while awaiting the advent of endogenous hormone changes and diagnostic confirmation. A number of drug regimens have been used in boys, but I suggest parenteral androgen preparations, which can be given safely over 1–2 yr or more. In fact, the longer time frame has become increasingly attractive as more experience has been gained.

These recommendations are a stopgap as we await more information regarding the behavioral implications of such suggested treatment. In the current setting of increased somatotropin usage for growth disorders, sex steroids appear as attractive therapeutic alternatives in selected patients who present with short stature and pubertal delay. In the more numerous boys who likely have constitutional delay, the clinician should consider trial treatment with testosterone analogues for periods of 1–2 yr while ruling out permanent hypogonadotropism with certainty. Not discussed in this review is the great importance of frequent consultations with parents regarding psychosocial problems and the need for psychological referral (and support) in many patients.

Acknowledgments

Appreciation is extended for preliminary data presentation to Pennsylvania State University colleagues Vernon Chinchilli, Jordan Finkelstein, and Elizabeth Susman.

References

1. **Adan L, Souberbielle JC, Brauner R.** 1994 Management of the short stature due to pubertal delay in boys. J Clin Endocrinol Metab. 78:478–482.
2. **Albanese A, Stanhope R.** 1995 Investigation of delayed puberty. Clin Endocrinol. 43:105–110.
3. **Crowne EC, Wallache WHB, Moore C, Mitchell, Robertson WR, Shalet SM.** 1995 Degree of activation of the pituitary-testicular axis in early pubertal boys with constitutional delay of growth and puberty determines the growth response to treatment with testosterone or oxandrolone. J Clin Endocrinol Metab. 80:1869–1875.
4. **Demir A, Dunkel L, Stenman UH, Voutilainen R.** 1995 Age-related course of urinary gonadotropins in children. J Clin Endocrinol Metab. 80:1457–1460.
5. **Finkelstein JS, Klibanski A, Neer RM.** 1996 A longitudinal evaluation of bone mineral density in adult men with histories of delayed puberty. J Clin Endocrinol Metab. 81:1152–1155.
6. **Finkelstein JW, Susman EJ, Chinchilli V, et al.** 1995 Testosterone (T) or conjugated estrogen (E) cause increases in aggressive behavior in hypogonadal boys or girls. Pediat Res. 37:88A (Abstract 515).
7. **Ghai K, Cara JF, Rosenfield RL.** 1995 Gonadotropin releasing hormone agonist (nafarelin) test to differentiate gonadotropin deficiency from constitutionally delayed puberty in teenage boys – A clinical research center study. J Clin Endocrinol Metab. 80:2980–2986.
8. **Knorr D, Bidlingmaier F, Butenandt O, Fendel H, Ehrt-Wehle R.** 1974 Plasma testosterone in male puberty. Acta Endocrinol. 75:181–195.
9. **Kulin H, Demers L, Chinchilli V, Martel J, Stevens L.** 1994 Usefulness of sequential urinary follicle-stimulating hormone and luteinizing hormone measurements in the diagnosis of adolescent hypogonadotropism in males. J Clin Endocrinol Metab. 78:1208–1211.
10. **Kulin HE.** 1994 The assessment of gonadotropins during childhood and adolescence: An ongoing struggle. The Endocrinologist. 4:279–285.
11. **Lemcke B, Zentgraf J, Behre HM, Kliesch S, Bramswig JH, Nieschlag E.** 1996 Long-term effects on testicular function of high-dose testosterone treatment for excessively tall stature. J Clin Endocrinol Metab. 81:296–301.
12. **Manasco PK, Umbach DM, Muly SM, et al.** 1995 Ontogeny of gonadotropin, testosterone, and inhibin secretion in normal boys through puberty based on overnight serial sampling. J Clin Endocrinol Metab. 80:2046–2052.
13. **Salehian B, Wang C, Alexander G, et al.** 1995 Pharmacokinetics, bioefficacy, and safety of sublingual testosterone cyclodextrin in hypogonadal men: Comparison to testosterone enanthate – A clinical research center study. J Clin Endocrinol Metab. 80:3567–3575.
14. **Susman EJ, Petersen AC.** Hormones and behavior in adolescence. In: McAnarney ER, Kreipe RE, Orr DP, Comerici GD eds. Textbook of adolescent medicine. New York: Saunders Publishing; 125–130.
15. **Wilson DM, McCauley E, Brown DR, Dudley R, and the Bio-Technology General Corporation Cooperative Study Group.** 1995 Oxandrolone therapy in constitutionally delayed growth and puberty. Pediat. 96:1095–1100.
16. **Wu FCW.** 1995 GnRH pulse generator activity during human puberty. In: Plant TM, Lee PA, eds. The neurobiology of puberty. Bristol, Journal of Endocrinology Ltd; 185–187..
17. **Wyatt DT, Mark D, Slyper A.** 1995 Survey of growth hormone treatment practices by 251 pediatric endocrinologists. J Clin Endocrinol Metab. 80:3292–3297.