

David P. Guo and Michael L. Eisenberg

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## 9.1 Puberty

Puberty refers to the biological changes that occur as one matures into a young adult. While cognitive, psychological, and social changes may occur during this period of adolescence, puberty in the clinical sense commonly refers to the development of reproductive capacity and secondary sexual characteristics. Specifically, the child begins to secrete increasing amounts of sex hormones and produce mature gametes.

Changes to the hypothalamic-pituitary-gonadal axis bring about the effects of puberty. At puberty, the hypothalamus begins to secrete gonadotropin-releasing hormone (GnRH) in a pulsatile fashion, which leads to pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the Leydig cells in the testes to produce testosterone and other androgens, while FSH stimulates Sertoli cells to produce substances that promote gametogenesis [1].

Puberty normally follows a predictable sequence of events. The first sexual change is an increase in testicular size. Next, there is an increase in penile length and then the development of pubic hair. By convention, sexually maturity is rated according to the Tanner Staging Chart (Table 9.1), which classifies the stages of puberty from 1 to 5 according to genital changes (penile length, testicular volume) and pubic hair distribution. Boys progress from prepubertal stage 1, characterized by the absence of genital growth and pubic hair, to mature adult stage 5, during which the genitalia has reached adult size and pubic hair is robust and extends to the medial thigh. Traditionally, it was thought that nocturnal seminal emissions (spermarche) occur after the development of pubic hair. However, a longitudinal study of 40 boys using spermaturia to evaluate spermarche found a wide variation

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D.P. Guo, M.D. • M.L. Eisenberg, M.D. (✉)  
Department of Urology, Stanford University School of Medicine,  
300 Pasteur Drive, S-287, Stanford, CA 94305, USA  
e-mail: [davidguo@stanford.edu](mailto:davidguo@stanford.edu); [eisenberg@stanford.edu](mailto:eisenberg@stanford.edu)

**Table 9.1** Tanner stages of puberty

Stage	Pubic hair	Genitalia
I	No pubic hair	Penis, testes similar size/proportion as in early childhood
II	Minimal, downy hair at base of penis	Testes have grown, scrotal texture changes
III	Darker, more coarse hair spreads over pubic region	Penile length increases; testes continue to grow
IV	Adult-type hair distributed across pubic region (does not reach thighs)	Penile length and girth increase; continued testis growth with darkening of scrotum
V	Adult-type hair that extends to medial surface of thighs	Adult size penis and testes

testicular size (median 11.5 mL, range 4.7–19.6 mL) and Tanner stage (median 2.5, range 1–5) [2].

While the sequence of pubertal events is predictable, there are fluctuations in the age of onset and pace of development. In a study of 228 British boys from 1970, Tanner and colleagues found the average onset of puberty to be 11.6 years (range 9.5–13.5 years) and the average time to completion of puberty over 3 years (range 1.8–4.7 years) [3]. More recent data on 4131 American boys indicated an earlier onset of puberty: 9.14 years for African American, 10.14 years for non-Hispanic white males, and 10.04 years for Hispanic males [4]. With this new data, it is possible that the current clinical norm (average age of puberty 11.5 years, range 9–14 years) will undergo an adjustment in the coming years.

In addition to sexual changes, other physiologic transitions occur during puberty. Skeletal maturation is accelerated due to the production of sex hormones. The secretion of testosterone also stimulates the release of growth hormone (GH), and the release of GH influences insulin-like growth hormone (IGF). As a result, there is increased bone growth, along with changes in weight and body composition. In fact, the classic change in voice occurs due to the differential effect of testosterone on the growth of the wide bones of the larynx [5].

Several medical issues may become apparent with the onset of puberty. Gynecomastia may be a bothersome manifestation in about 50 % of boys but is usually self-limited and usually resolves within a year [6]. The development of myopia often occurs during puberty due to changing axial length of the eyes and appears to be most correlated with the growth spurt [7]. The prevalence and severity of acne increases with the onset of puberty [8]. Psychological, emotional, and behavioral issues may also manifest at puberty.

### 9.1.1 Clinical Implications

The timing of puberty and whether a child is developing normally are frequent areas of concern that a clinician should be prepared to address. The onset of puberty is thought to coincide with central nervous system maturation, which results in the

gradual increase of pulsatile secretion of GnRH. The onset of puberty is determined heavily by genetics, but factors including ethnicity, nutritional status, medical conditions, and environmental exposures also affect the timing of puberty. When the onset of puberty occurs 2.5 standard deviations earlier or later than the average age of onset, clinicians should be suspicious for an underlying pathology.

Precocious puberty should be suspected if a male child develops symptoms of puberty prior to age 9 (although this number has been debated due to recent findings that the age of puberty is declining in the USA). Precocious puberty may be central (gonadotropin dependent) or peripheral (gonadotropin independent). Central causes depend on the hypothalamic-pituitary-gonadal (HPG) axis and may result from idiopathic early maturation of the HPG axis or development of a hormone-secreting central tumor. Peripheral causes include hormone-secreting testicular or adrenal tumors and exogenous steroid administration.

Delayed puberty should be suspected if the patient does not show signs of testicular volume growth or pubic hair growth until after age 14. Constitutional delay of puberty, in which there is no pathology and the patient undergoes puberty at the later end of the spectrum, accounted for 63 % of cases of delayed puberty in a large academic series of 158 boys [9]. The other main causes are functional hypogonadotropic hypogonadism, in which puberty is delayed but occurs spontaneously despite an underlying condition; idiopathic delayed puberty, in which a cause is not found; or permanent hypogonadism (hypergonadotropic or hypogonadotropic).

Patients who are suspected to have precocious puberty or delayed puberty should be referred for evaluation by a pediatric endocrinologist, who may provide treatment according to underlying etiology.

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## 9.2 Fertility

Men become fertile after the maturation of their gametes during puberty. In contrast to women, who experience an accelerated rate of fertility decline by age 35, there is no limit to fertility as long as a man still produces sperm. However, recent data does suggest a slight decline in fertility with male age [10].

The World Health Organization (WHO) defines infertility as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [11]. Studies have shown that up to 15 % of couples experience problems with fertility [12]. In 20 % of these situations, there is a male factor that is primarily responsible for infertility. In 30 % of situations, there are both male and female factors involved. Therefore, 50 % of infertility cases involve the male [13, 14].

A useful framework for classifying the causes of male infertility is to consider pre-testicular, testicular, and post-testicular causes. Pre-testicular causes refer mainly to endocrine dysfunction or any medical conditions or exposures that secondarily affect testicular function. Testicular causes refer to the failure of normal sperm production despite a favorable hormonal environment. Factors such as varicocele, cryptorchidism, genetic defects, trauma, infection, or malignancy may cause

primary testicular failure. Post-testicular causes refer to anatomic or functional problems with releasing sperm, such as obstruction of the vas deferens or ejaculatory ducts.

### 9.2.1 Clinical Implications

A thorough medical history is vital to the evaluation of male infertility. It is important to note the age of the female partner, since the age of 35 is considered advanced maternal age, and the woman should also receive a separate evaluation. Aspects of the couple's relationship should be investigated, including the length of time in active attempt to conceive, the timing of coitus in relation to the woman's mid-ovulatory cycle, and whether either partner been involved in a previous pregnancy. The medical history should investigate childhood diseases or urologic problems such as a varicocele, cryptorchidism, hypospadias, and any instances of genitourinary trauma or infection. Surgeries in the inguinal, pelvic or genital region may disrupt the reproductive tract. Medications, most notably exogenous steroids, as well as certain antibiotics can disrupt spermatogenesis. Sexually transmitted diseases may result in scarring and obstruction of the reproductive tract. Exposures, both recreational and environmental, should be recorded. Tobacco [15], marijuana, and alcohol use have been associated with semen abnormalities, as well as certain pesticides [16], sauna exposure [17], and laptop usage [18].

The general physical exam, including stature, distribution of hair, and presence of gynecomastia, may provide clues about the patient's androgen status. The genitourinary exam should focus on the phallus and scrotal contents. Anatomical abnormalities of the phallus, including hypospadias and penile torsion, may hinder fertility. For the scrotal examination, an orchidometer is a useful tool to estimate volume and may diagnose testicular atrophy: the size of the adult testes is on average: 4.6 cm long by 2.6 cm wide and 18–20 mL. In addition, the spermatic cord should be palpated to confirm presence of the vas deferens bilaterally and also to evaluate for a varicocele, which is a testicular engorgement of the veins that supply the testes. While 15 % of the male population has a varicocele, 40 % of men with infertility have a varicocele.

Semen analysis should be performed in a male fertility evaluation. The WHO revised its of standards in 2010 for minimum standards of semen quality consistent with fertility using data from over 4500 men from 14 countries [11]. These 5th edition criteria are ejaculate volume ( $>1.5$  mL), sperm concentration ( $>15 \times 10^6$  sperm/mL), vitality ( $>58$  %), progressive motility ( $>32$  %), total motility ( $>40$  %), and morphology (4 % based on Kruger strict criteria) (Table 9.2). Because semen quality can vary widely for the individual male, two samples taken at least 7 days apart are recommended. While semen analyses are useful for some diagnoses, about half of men from infertile couples do not have abnormalities on standard semen analysis [19]. Moreover, men with abnormal semen parameters often achieve pregnancy.

In addition to a semen analysis, serum testosterone and FSH are routinely sent. Low FSH and low testosterone indicate hypogonadotropic hypogonadism, which

**Table 9.2** WHO 5th edition semen parameter guidelines, 2010

Measurement	Lower limit	95 % Confidence intervals
Volume (mL)	1.5	1.4–1.7
Sperm count (million per ejaculate)	39	33–46
Concentration (million/mL)	15	12–16
Vitality (live %)	58	55–63
Progressive motility (PR, %)	32	31–34
Total motility (PR+NP, %)	40	38–42
Normal morphology (%)	4	3.0–4.0

may be congenital or iatrogenic (e.g., steroids). High FSH and low testosterone indicate primary hypogonadism due to testicular failure. Further endocrine studies may be necessary if there are abnormalities in these parameters or if there are additional symptoms suggestive of endocrine dysfunction. These include prolactin, LH, and estradiol levels. For example, hyperprolactinemia may be caused by medications, systemic disease, or a pituitary tumor.

An estimated 15 % of infertile men with azoospermia or severe oligospermia have a genetic abnormality. A family history or congenital absence of the vas deferens (CAVD) may indicate cystic fibrosis, since 2 % of infertile males have cystic fibrosis and 90 % of patients with CAVD have cystic fibrosis. In addition, polymerase chain reaction can detect several deletions on the Y chromosome that have been associated with infertility. Karyotype analysis can identify chromosomal causes of infertility, such as Klinefelter's syndrome, in which there is an extra X chromosome.

## 9.2.2 Treatment

Modern treatment for fertility has drastically increased the fertility rate for patients.

### Medical Therapies

For hypogonadotropic hypogonadism, treatment with human chorionic gonadotropin (hCG) and FSH can induce testosterone and stimulate spermatogenesis [20]. For idiopathic infertility, treatment with clomiphene citrate, an estrogen antagonist, has been attempted, but without successful improvement of pregnancy rate [21]. A large meta-analysis of 48 RCTs that study the effect on infertile men of antioxidants, including zinc, vitamin E, vitamin C, L-carnitine, and *N*-acetylcysteine, on fertility have suggested an improvement in live birth rate, though the quality of evidence was deemed to be low [22].

### Surgical Therapies

A variety of surgical interventions are available, depending on the etiology of infertility. For infertile males with varicocele, a varicocelectomy can be performed via a laparoscopic or open approach (inguinal, subinguinal, or retroperitoneal) as

well as through interventional radiologic procedures at some centers. For men who have a prior vasectomy or another cause of vasal obstruction, vasal aspiration may be performed to retrieve sperm for one-time use. Microscopic reconstruction may also be performed, with success rates between 70 and 90 % [23]. The vas deferens may be reconnected (vasovasostomy) or the vas deferens can be connected to the epididymis (epididymovasostomy). For men with nonobstructive azoospermia, the use of microscopic techniques was shown to improve the yield of surgical extracted sperm from 45 to 63 % [24]. Furthermore, a review of 1127 men with azoospermia who underwent microdissection testicular sperm extraction demonstrated comparable successful retrieval rate (55 %) even in severe testicular atrophy (<2 mL) [25].

### Assisted Reproductive Therapies

The three main assisted reproductive strategies are intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI). The selection of technique depends on the number of viable sperm available and anatomic considerations for the female partner (Table 9.3).

IUI refers to the manual injection of a sperm pellet within the uterus, bypassing the cervical mucosa; this normally requires 5–40 million motile sperm. The success rate per cycle has been reported to be 5–16 % per cycle. IVF requires an intensive and coordinated process involving both partners. The woman undergoes hormonal stimulation, and subsequently her eggs are harvested transvaginally via ultrasound guidance. Sperm are provided by the male partner (ejaculated or surgically retrieved) or from a sperm donor. The eggs and sperm are mixed in vitro, the embryos are incubated for several days, and the best quality embryos are transferred to the uterus. When sperm counts are low (as in surgical retrieval), ICSI is employed. In this procedure, a single viable sperm may be microinjected into an oocyte, and then the fertilized egg is implanted into the uterus. This advanced technique has revolutionized treatment for infertile men previously considered sterile.

**Table 9.3** Three primary assisted reproductive technologies

Technique	Description	Sperm required
Intrauterine insemination (IUI)	Manual injection of sperm pellet into uterus	5–40 million
In vitro fertilization (IVF)	Mixing egg and sperm outside of body, using eggs harvested via ultrasound aspiration and ejaculated or surgically retrieved sperm	0.5–5 million
Intracytoplasmic sperm injection (ICSI)	Single viable sperm (often surgically retrieved) is microinjected into the oocyte, and fertilized egg is implanted	1 or more

## 9.3 Andropause

The term “andropause” has become popularized in the media as the male equivalent of “menopause.” Menopause refers to the cessation of ovulation, which arrives with a significant decrease in estrogen and multiple medical implications for aging women. Men do not undergo a parallel process, although they do undergo changes in hormone levels as they age. The mechanism and etiology of declining testosterone levels in men are not completely clear, but epidemiologic data suggests that total testosterone level appears to decline at a relatively constant rate of 3.2 ng/dL (about 0.5–1 %) per year after age 30 [26].

As a clinical entity, andropause may be referred to as “late onset hypogonadism” (LOH), although this has also been termed testosterone deficiency syndrome (TDS). According to the American Endocrine Society guidelines, this is defined as the signs and symptoms of testosterone deficiency confirmed by two early morning measurements of total serum testosterone level that fall below the normal range of 300–950 ng/dL (10.4 to 32.9 nmol/L) [27]. The prevalence of testosterone deficiency syndrome is highly influenced by age: an epidemiological study of 1475 black, Hispanic, and white men found symptomatic androgen deficiency in 3.1–7.0 % of men from ages 30–69, in comparison to 18.4 % of men from ages 70–79 [28].

### 9.3.1 Clinical Implications

The symptoms of low testosterone are varied and nonspecific, including decreased sexual function, fatigue, diminished neurologic function, decreased mobility, and other physical changes. Changes in sexual function are the most specific and include low libido, erectile dysfunction, and decreased pleasure. The patient may exhibit neurologic symptoms: increased irritability, decreased concentration, or inability to sleep. Decreased muscle mass, energy level, and bone mineralization may result from decreased testosterone levels, and these conditions may translate to decreased mobility or activity level.

In order to diagnose testosterone deficiency syndrome, a total serum testosterone and a serum free testosterone should be measured. Testosterone is normally bound by sex hormone-binding globulin (SHBG), which is produced by the liver. Testosterone is active only in its free form. Depending on the assay used, a level of 300–950 ng/dL (10.4 to 32.9 nmol/L) is considered normal. Testosterone should be performed early in the morning; after the recording of a low level, this should be repeated on a separate occasion due to the inherent variability. Although the symptoms of testosterone deficiency are nonspecific, the association of these symptoms with a low serum testosterone measurement is adequate to diagnose clinical testosterone deficiency. Following diagnosis, the patient should be screened for chronic illnesses including hypertension, hyperlipidemia, obesity, and diabetes. He should also be screened for obstructive sleep apnea and thyroid disease. His mobility and activity level should be assessed.

Next, the etiology should be considered. The first principle of treatment is to rule out reversible causes of low testosterone. These include obstructive sleep apnea, hyperthyroidism, the use of certain medications (e.g., opiates, cimetidine, ketoconazole), depression, and excessive alcohol intake. In particular, the disorder may also have to do with an alteration in the amount of SHBG, which may be affected by the liver or the thyroid. Obesity may lower SHBG levels and therefore lower total testosterone levels. When other causes of low testosterone have been ruled out, the clinician may begin discussion regarding testosterone replacement.

### 9.3.2 Treatment

There are many forms of testosterone supplementation. We highlight the most commonly used. Testosterone supplementation therapy (TST) may be administered in the form of intramuscular injections in either short- or long-term formulations. It may also be administered transdermally in gel or patch form. This must be applied in a nonexposed area to prevent transfer to other people (especially intimate partners or young children). An alternative formulation is the testosterone pellet (Testopel™), which is injected beneath the skin in an office procedure on a monthly basis. Other formulations include intranasal gel, buccal patches, and oral therapies.

#### Controversies of Testosterone Treatment

Testosterone treatment has been shown to increase libido [29], muscle strength [30], and bone mineral density [31] while decreasing waist circumference [32]. However, known risks also exist including erythrocytosis, infertility, acne, gynecomastia, balding, and worsening obstructive sleep apnea [27]. Overall, the use of testosterone replacement was formerly seen as beneficial in older men, but it has lately has been controversial due to reports of a negative cardiovascular impact. While some observational studies have demonstrated an overall benefit with testosterone supplementation, other studies have suggested harm.

An observational study of veterans age 40 and above with low testosterone demonstrated a lower all-cause mortality rate (10.3 % vs. 20.7 %,  $p < 0.0001$ ) for men who had received testosterone supplementation therapy versus those who had not [33]. However, in a randomized control trial of men over age 65 with limited mobility and low testosterone, a higher number of cardiovascular events were seen in men who received testosterone gel, resulting in the early termination of the trial [34]. While this study had accrued limited numbers and applied to select group of chronically ill elderly men, the findings raised strong concerns about the usage of testosterone supplementation with regard to cardiovascular risk. Subsequent large database studies were conducted that also raised concern of increased risk of mortality in men who had undergone coronary angiography [35] and increased risk of nonfatal myocardial infarction in men who were receiving testosterone supplementation [36].

Our understanding of the impact of testosterone on prostate cancer has also evolved with time. The current guidelines of the American Endocrine Society



recommend against the usage of testosterone replacement in men with prostate cancer [27]. Because androgen deprivation therapy is used to treat high-risk prostate cancer, it is inferred that increased testosterone levels may increase the risk of prostate cancer development or progression. Furthermore, trials of 5-alpha reductase inhibitors, which lower intracellular dihydrotestosterone (DHT) levels, reduce the risk of prostate cancer diagnosis (PCPT and REDUCE trials) and reduce the progression of prostate cancer in men on active surveillance (REDEEM trial) [37–39]. TST, which increases intracellular DHT, might increase the risk of prostate cancer.

However, no large, prospective trials have demonstrated an increased prostate cancer-specific mortality with TST in men on active surveillance, post-prostatectomy, or postradiation setting [40]. One theory that has been advanced has been the “saturation hypothesis” [41]. In this model, prostate cancer is thought only to be responsive to a threshold level of testosterone, and an increased amount would not necessarily result in the development of prostate cancer. In practice, the use of testosterone replacement, even in men with a history of prostate cancer both treated and untreated, has been acceptable to urologists and patients with no signs of adverse consequences [42–45].

The long-term effects of testosterone are incompletely characterized. The results from prior studies are at times in conflict, and the numbers in clinical trials have been small. Therefore, testosterone, as with all medical therapies, should be prescribed with consideration of the patient’s individual risk factors after a thorough discussion of the risks and benefits.

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