13.6.2 Disorders of male reproduction and male hyp

13.6.2 Disorders of male reproduction and male hypogonadism 2386

section 13 Endocrine disorders 2386 In women with hirsutism and menstrual disturbance, the most likely diagnosis is again PCOS. In such cases, however, it is legit- imate to extend biochemical tests to include measurements of gonadotropins and, in amenorrhoeic women, prolactin and oestra- diol. Further investigations are necessary in those patients with a short history of hirsutism (particularly if this is severe), with symp- toms suggesting other endocrine disorders (e.g. Cushing syndrome) and/or those with a high serum testosterone (loosely defined as a level more than twice the upper limit of the normal range for the laboratory). In female patients with a serum testosterone concen- tration in the normal male range (>10 nmol/litre), the presence of an androgen-secreting tumour must be excluded. Imaging of the ovaries and adrenals by MRI is important. In experienced hands, ultrasonography of the adrenals and, particularly the ovaries may also be helpful. Selective catheterization of adrenal or ovarian veins to localize suspected a suspected tumour is difficult to execute and rarely informative. Measurement of dehydroepiandrosterone sul- phate (DHEAS) is a useful specific index of adrenal function in patients with a suspected androgen-secreting tumour but it is less helpful as a routine test in hirsute patients. The prevalence of nonclassical CAH is very low (<1% of cases of hirsutism) so it is not necessary to routinely measure basal and ACTH-stimulated concentrations of 17-hydroxyprogesterone to screen for this disorder. However, it is appropriate to do so in women with severe hirsutism and a raised serum testosterone. Management of hirsutism The approach to the management of women with hirsutism is described earlier in the section about PCOS. The principles of symptomatic management are similar in women with idiopathic hirsutism. In those with a specific underlying diagnosis, treatment is directed towards that primary disease or disorder. For example, removal of a pituitary corticotroph adenoma or an ovarian tumour is a very effective way of treating hirsutism. FURTHER READING Baird DT (1983). Prediction of ovulation: biophysical, physiological and biochemical coordinates. In: Jeffcoate SL (ed) Ovulation: methods for its prediction and detection, pp. 1–17. John Wiley,

Chichester. Berga SL, Loucks TL (2005). The diagnosis and treatment of stress- induced anovulation. Minerva Ginecol, 57, 45–54. Boehm U, et al. (2015). Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism—pathogenesis, diagnosis and treatment. Nat Rev Endocrinol, 11, 547–64. Dunaif A (2016). Perspectives in polycystic ovary syndrome: from hair to eternity. J Clin Endocrinol Metab, 101, 759–68. Gillam MP, et al. (2006). Advances in the treatment of prolactinomas. Endocr Rev, 27, 485–534. Gougeon A (1996). Regulation of ovarian follicular development in primates: facts and hypotheses. Endocr Rev, 17, 121–54. Hardy K, et al. (2000). In vitro maturation of oocytes. Br Med Bull, 56, 588–602. Jayasena CN, Franks S (2014). The management of patients with poly- cystic ovary syndrome. Nat Rev Endocrinol, 10, 624–36. Koulouri O, Conway GS (2008). A systematic review of commonly used medical treatments for hirsutism in women. Clin Endocrinol (Oxf), 68, 800–5. Norman RJ, et al. (2007). Polycystic ovary syndrome. Lancet, 370, 685–97. Teede HJ, et al. (2018). Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human Reproduction, 33, 1602–18. Webber L, et al. (2016). ESHRE guideline: management of women with premature ovarian insufficiency. Human Reproduction, 31, 926–37. 13.6.2 Disorders of male reproduction and male hypogonadism P.-M.G. Bouloux ESSENTIALS The adult testis performs two principle functions: the synthesis and secretion of androgens, and the production of male germ cells, the spermatozoa. Gonadotrophin releasing hormone, released from the hypothalamus, stimulates pituitary release of luteinizing and follicle-stimulating hormones (LH and FSH). LH acts on Leydig cells of the testes promoting synthesis and release of the principle male androgen testosterone. Testosterone is essential for male sexual differentiation, growth, and function of the male genital tract, secondary sexual char- acteristics, sexual potency, and production of spermatozoa. Hypogonadism Hypogonadism may be due to disorders of the pituitary/hypothal- amus (secondary or hypogonadotropic hypogonadism) or testes (primary or hypergonadotropic hypogonadism). Clinical features—symptoms and signs depend on the age of onset of androgen deficiency. Prepubertal presentation is with sexual in- fantilism, delayed puberty, and eunuchoidal body proportions. Postpubertal presentation is with diminished sex drive and erection, loss of ejaculation, muscle atrophy, poor stamina, decreased sec- ondary sexual hair, decreased shaving frequency, and regression of spermatogenesis (reduced testicular volume). Diagnosis—hypogonadism is confirmed by low serum testos- terone, best measured between 08.00 and 09.00 h. Measurement of Table 13.6.1.7 Guide to investigation of hirsutism Presenting features Investigations Mild, chronic hirsutism, regular cycles Testosterone, ultrasound of ovaries Moderate hirsutism and/or cycle disturbance Testosterone, (LH, FSH), ultrasound of ovaries Severe hirsutism and/or short history and/or testosterone

> “ 5 nmol/litre DHEAS, 17-hydroxyprogesterone, dexamethasone suppression test, 24 h urine free cortisol ovarian &/or adrenal imaging fasting glucose/insulin

13.6.2 Disorders of male reproduction and male hypogonadism 2387 LH and FSH differentiates between primary (high gonadotrophins) and secondary (low gonadotrophins) hypogonadism. Specific causes of primary gonadal failure include Klinefelter’s syndrome (eunuchoid proportions, typical karyotype 47XXY) and dystrophia myotonica, and of secondary gonadal failure in- clude Kallmann’s syndrome (anosmia, red–green colour blindness, synkinesis, nerve deafness, cleft lip or palate, and renal malforma- tions). Cryptorchidism, the absence of one or both testes from the

scrotum and the commonest birth defect of the male genitals, results from the failure of the testis to descend during fetal development from an abdominal position into the scrotum and is associated with increased risk of testicular cancer. Management—the aims of treatment are to: (1) relieve the symptoms of androgen deficiency; (2) prevent the long-term consequences of androgen deficiency such as osteopenia;
(3) reproduce physiological circulating and tissue levels of testos- terone, dihydrotestosterone, and oestradiol; (4) induce fertility, if required, in hypogonadotropic patients; (5) treat any specific underlying diseases. The mainstay of treatment is androgen re- placement therapy. Infertility Male infertility may affect 5% of men of reproductive age and is caused by a heterogeneous group of disorders. The commonest cause (60% of cases) is ‘idiopathic’ azoo/oligozoospermia, although many cases are now recognized as due to discrete gene defects asso- ciated with impaired spermatogenesis. Other causes include crypt- orchidism, testicular tumours, genital tract infection, obstructive azoospermia, and sperm autoimmunity. Laboratory investigation—conventional parameters of the semen analysis provide a semiquantitative index of fertility potential. Measurement of plasma testosterone, LH, FSH, and chromosome karyotyping is indicated in some cases. Management—no medical treatment has been shown to im- prove fertility in subfertile men. Assisted conception techniques are increasingly applied to overcome idiopathic male infertility, including intrauterine insemination, In vitro fertilization, and micro- injection of a single live spermatozoon directly into harvested oo- cytes, which is the treatment of choice for severe oligozoospermia. Cryopreservation of semen should be offered to all men of repro- ductive age before anticancer chemotherapy, orchidectomy, or tes- ticular irradiation. Physiology of the hypothalamo-pituitary-
testicular axis The testes The adult testis performs two principle functions: the synthesis and secretion of androgens, and the production of male germ cells, the spermatozoa. The testicular parenchyma is surrounded by a solid capsule (tunica albuginea) and consists of seminiferous tu- bules in which gametes are produced. Septa of connective tissue divide the testis into 200–300 lobules which coalesce to form the rete testes. Each lobule contains two to three seminiferous tubules and each testis contains 600–900 seminiferous tubules. Testicular function is under the regulation of the hypothalamo-pituitary axis (Fig. 13.6.2.1). Central control of testicular function The septo-preoptic region of the hypothalamus contains about 2000 dispersed gonadotrophin releasing hormone (GnRH) neurons, whose nerve endings converge on the capillary plexus of the me- dian eminence, where episodic neurosecretion of the 10 amino acid decapeptide GnRH occurs every 90–120 minutes in the adult. The episodic secretion of GnRH represents an intrinsic property of GnRH neurones, a basic rhythm essential for correct functioning of the gonadotroph that is modulated by numerous neurotransmit- ters, which modulate pulse amplitude and frequency. Prolactin is a potent negative modulator of GnRH pulse frequency. GnRH in turn stimulates the gonadotrophs cells of the anterior pituitary to synthesize and secrete the glycoproteins luteinizing and follicle- stimulating hormones (LH and FSH). These hormones are secreted in an episodic manner, entrained by the pulsatile GnRH secretion. LH acts on Leydig cells of the testes promoting synthesis and release of the principle male androgen testosterone. Negative feedback con- trol of LH secretion by testosterone is in part mediated by aroma- tization into oestradiol by the hypothalamus. By contrast, FSH binds to FSH receptors of the Sertoli cells of the testes, leading to the elab- oration of inhibin B, which negatively feeds back on pituitary FSH secretion. Locally produced activin in the pituitary, stimulates FSH secretion. There are no FSH receptors on the germ cells themselves (Fig. 13.6.2.2). In the adenohypophysis, GnRH binds to a specific G-protein coupled receptor on gonadotrophs, initiating gene expression of the α and β subunits of FSH and

LH and their secretion by induction of inositol 1,4,5-triphosphate, mobilization of intra- cellular calcium, and stimulation of calcium influx. Androgens reduce the expression of GnRH receptors. Experimentally, con- tinuous exposure of gonadotrophs to exogenous GnRH leads to GnRH receptor desensitization and subsequent profound suppression of gonadotrophin secretion and therefore gonadal steroid production. This desensitizing property of continuous GnRH exposure on GnRH receptors is exploited clinically in the use of GnRH super-active analogues to produce effective med- ical castration in conditions such as prostatic carcinoma and endometriosis. Mode of action of gonadotrophins The glycoproteins LH and FSH comprise noncovalently bound α and β chains, which form a heterodimer. The α chain (encoded on chromosome 6) is common to all glycoprotein hormones, whereas the β chain is specific (LH β chain chromosome 19; FSH β chain chromosome 11); the biological activity of these glycoprotein hormones is mediated by the β chain, and isolated subunits and homodimers have no biological activity. The carbohydrate content of glycoprotein hormones differs significantly and influence the ter- tiary structure of these molecules, exerting a powerful influence on their biological half-life, binding to specific receptors, and also intra- cellular signal transduction after receptor binding in target cells. A high concentration of sialic acid residues prevents their metab- olism in the liver; this prolongs the half-life and biological activity

section 13 Endocrine disorders 2388 of FSH. LH has a half-life of 20 minutes whereas FSH has a half-life of 3 hours. LH binds to its specific receptor on Leydig cells, and via the action of adenyl cyclase, induces cAMP formation, effecting an increase in formation of intracellular cholesterol and gene expres- sion of enzymes involved in steroidogenesis, in particular the key enzyme 20,22-desmolase, which initiates the formation of testos- terone by cleavage of the cholesterol side chain. The feedback control of LH production in man is mediated via testosterone and its metabolite oestradiol. Testosterone has an in- hibitory effect on GnRH neurons with only a minor effect on the gonadotroph, whereas oestradiol exerts negative feedback at both hypothalamic and gonadotroph levels. FSH binds to its receptor on the Sertoli cells, and induces activity of the aromatase enzyme which converts testosterone into oestradiol. It also induces formation of inhibin B and activin. Inhibin B is a heterodimer composed of α and β subunits; there are two variants (β α, and β β). Hetero- and homodimers of the β chain are called activin A and B, respectively. Inhibin is an important component in the negative feedback regu- lation of FSH secretion, and in isolated functional disturbances of the Sertoli cells (Sertoli cell only, following radiotherapy or chemo-therapy), low inhibin B levels are associated with elevation of FSH, while LH levels remain unchanged. Activins can stimulate FSH secretion at the pituitary level. Testosterone and E2 exert negative feedback on FSH via an effect on GnRH neurons. Spermatogenesis Spermatogenesis is a complex process involving both mitotic di- visions and meiosis processes, the latter the process whereby dip- loid spermatogonia become haploid spermatids (Fig. 13.6.2.3). Spermatids are transformed into flagellated spermatozoa, a pro- cess known as spermiogenesis. After spermiogenesis is complete, spermatozoa are released from the germinal epithelium into the epididymis with the fluid from the tubules. The entire process takes 60–72 days in the human. Sertoli cells are essential to the early devel- opmental stages of spermatogenesis, up to the stage of spermiation. Sertoli cells extend from the basement membrane of the semin- iferous tubules deep into the lumen. They express the androgen receptor and, under the influence of testosterone and FSH, secrete electrolytes and fluid into the lumen. In the postpubertal stage, spermatogenesis can be maintained without FSH by sufficiently high local testosterone concentrations alone. Sertoli cells form tight junctions with each other at their base, sealing the intercellular gaps, thereby forming the anatomical basis of the ‘blood-testes’ barrier. Hypothalamus Anterior pituitary Inhibin

Testes Second messenger Cell products Sertoli cell Sertoli cell Androgen-binding protein (ABP) (ABP) To body for secondary effects Testosterone (T) Leydig cells Spermatogonium – – – Tissue response Integrating centre KEY Efferent pathway Effector Spermatocyte GnRH LH T FSH
Fig. 13.6.2.1 Organization of hypothalamo-pituitary-testicular axis. GnRH is secreted in a pulsatile manner into the portal circulation and this in turn leads to pulsatile release of LH and FSH. FSH is required for spermatogenesis and inhibit B secretion from Sertoli cells, and LH, acting on Leydig cells promotes synthesis and release of testosterone. Inhibin B and testosterone (via oestradiol) participate in negative feedback regulation of gonadotrophin secretion

13.6.2 Disorders of male reproduction and male hypogonadism 2389 Spermatogonia are embedded between Sertoli cells; during sperm- atogenesis, developing cells migrate from the basement membrane to the lumen, where the spermatozoa are released. In the fetus, Sertoli cells produce the anti-Müllerian hor- mone (AMH), which prevents the development of the uterus and Fallopian tubes from the Müllerian duct during sexual differenti- ation in the male. AMH can be detected in serum until puberty and then levels fall. Spermatogenesis is a complex, repetitive series of cytodifferentia tion processes in the seminiferous epithelium, whereby cohorts of undifferentiated diploid germ cells (spermatogonia) proliferate and transform into the greatly expanded populations of haploid spermatozoa. The human testes produce around 200 million sperm- atozoa per day. Mitotic divisions of spermatogonial stem cells form subpopulations of spermatogonia which, at regular intervals of 16 days, differentiate into primary preleptotene spermatocytes to ini- tiate meiosis. Meiotic reduction divisions of spermatocytes generate round spermatids which are then transformed (spermiogenesis) into compact, virtually cytoplasm free, elongated spermatids. Condensed nuclear DNA forms the sperm head within an overlying HYP PRL KiSS-1 GnRH PIT Testosterone oestradiol LH FSH Inhibin B Testis Norepinephrine, Galanin-like peptide (GALP), glutaminergic, Neuropeptide Y (NPY) β-endorphin, corticotrophin releasing hormone (CRH), γ-amino butyric acid (GABA) Fig. 13.6.2.2 GnRH neurons are located in the hypothalamus in the septo-preoptic region and release GnRH at the median eminence capillary plexus. GnRH neutrons receive both stimulatory (norepinephrine, kisspeptin, galanin-like peptide (GALP), glutaminergic, neuropeptide Y (NPY)) as well as inhibitory inputs (β endorphin, corticotrophin-releasing hormone (CRH), γ-amino butyric acid (GABA)). Kisspeptin neurons express oestrogen, progesterone, and androgen receptors, and leptin receptors which are also expressed on NPY neurons. FSH, follicle-stimulating hormone; GABA, γ-amino butyric acid; GnRH, gonadotropin-releasing hormone; HYP, hypothalamus; KiSS-1, Kisspeptin; LH, luteinizing hormone; PIT, pituitary gland; PRL, prolactin; T, inhibitory signal; ↑, stimulatory signal. Spermatogonium 2n 2n 2n 1n 1n 1n 1n 1n 1n (a) Spermatogenesis Mitosis Primary spermatocyte Secondary spermatocyte Meiosis I Meiosis II Spermatid Spermiogenesis Spermatozoa (sperm) Peritubular cells (b) Sertoli cells Round spermatids Elongated spermatids Spermatogonia Leydig cells Spermatocytes Fig. 13.6.2.3 (a) Spermatogenesis. Spermatogonia are located on the basement membrane of the seminiferous tubules, wedged between Sertoli cells. They undergo mitosis into primary spermatocytes, which in turn undergo a meiotic division into secondary spermatocytes, and a after a second meiotic division, spermatids are formed. These undergo spermatogenesis into mature spermatozoa. (b) Cross section of a seminiferous tubule. (b) Reproduced from Wass JAH, Stewart PM, Amiel SA, Davies MJ (2011). Oxford textbook of endocrinology and diabetes, 2nd edn. By permission of Oxford University Press.

section 13 Endocrine disorders 2390 Golgi–derived acrosome and a tail (containing nine pairs of micro- tubules arranged around a central pair) capable of propelling, fla- gellar movements. Mature spermatozoa are released from Sertoli cell cytoplasm into the tubular lumen some 60 to 74 days after the initial development from spermatogonia. The control systems regulating germ-cell divisions and development are poorly understood. Testosterone and the androgen receptor Testosterone biosynthesis Testosterone is the most important steroid synthesized in the testes, 5–7 mg being produced by the Leydig cells of an adult man each day. Leydig cells have a large endoplasmic reticulum and copious mitochondria. The parent substance of testosterone biosynthesis is cholesterol, mainly synthesized by Leydig cells, only a small amount being taken up from the circulation. Cholesterol is stored in the form of esters in fat vacuoles in these cells, until further processing through a total of five enzymatic steps converting cholesterol (C27) through hydrolytic steps into testosterone (C19). The rate limiting step in testosterone biosynthesis is the conversion of cholesterol to pregnenolone, a process which occurs on the inner mitochondrial membrane where the cytochrome P450sc (sc, side-chain cleavage), 20, 22 desmolase, encoded on chromosome 15) enzyme catalyses three consecutive processes: hydroxylation on atom C20, followed by hydroxylation on atom C22, and thereafter cleavage between C20 and C22, thereby generating pregnenolone and isocaproic acid. This process depends on LH binding to the LH receptor, activation of adenylyl cyclase, generation of cAMP, and activation of protein kinase A. Pregnenolone is the parent steroid of all biologically ac- tive steroid hormones, and exits the mitochondrion by simple diffu- sion to undergo further modification on the endoplasmic reticulum. The Δ5 pathway leads to the initial C17 hydroxylation (via 17 α- hydroxylase) forming 17 α-hydroxypregnenolone. The weak an- drogens DHEA (dehydroepiandrosterone) and androstenediol are produced by the enzymes 17,20 desmolase, and 17-β hydroxysteroid dehydrogenase, respectively (Fig. 13.6.2.4). An additional step is the conversion of the less biologically active Δ5 steroids 17 α- hydroxypregnenolone, DHEA and androstenediol to the corres- pondingly more potent Δ4 steroids 17 α-hydroxyprogesterone, androstenedione, and testosterone, respectively, steps catalysed by the enzyme 3 β-hydroxysteroid dehydrogenase. This is effected by the initial oxidation of the 3β-hydroxy group to a ketone, followed by the subsequent transfer of the C5–C6 gene group from the B ring to the C4–C5 site on the A ring. Newly synthesized testosterone cannot be stored in the testes and is immediately released into the circulation via the spermatic vein and lymphatics. Testosterone transport in the blood The lipophilic molecule testosterone leaves the Leydig cell by diffu- sion, and in the blood is largely bound to transport proteins (98%), leaving approximately 2% free and biologically active. About 60% is transported via high affinity binding to the 92.5 KDa β globulin glycoprotein molecule SHBG (sex hormone binding globulin), en- coded on chromosome 17, whereas approximately 38% is loosely bound to albumin. SHBG circulates as a homodimer with two binding sites for steroids. It is predominantly synthesized in the liver, with a little manufactured by the mammary gland and prostate. SHBG may also bind to specific membrane receptors, and account for the rapid nongenomic effects of testosterone and oestradiol (E2). SHBG binds testosterone (T) with greater affinity than oestradiol (E2), and conditions where SHBG are elevated will lead to a shift in the free E2 to T ratio. Several factors regulate SHBG concentration as shown in Table 13.6.2.1. Some conditions, such as cirrhosis due to hepatitis C, can cause significant rises in SHBG concentrations, thereby reducing free T concentrations; when inadequately com- pensated by a rise in LH, a state of hypogonadism will ensue. HO Cholesterol 1 4 HO HO HO HO HO OH OH O OH Pregnenolone 17-OH-Pregnenolone 17-OH-Progesterone Progesterone Dehydroepi- androsterone 5-androstene- 3β, 17β-diol Oestradiol 5α-dihydrotestosterone Testosterone Androstenedione C O C O C O OH OH OH O O O O CH3 CH3 CH3

C O O CH3 4 4 4 3 3 5 6 2 2 2 2 Fig. 13.6.2.4 Steroid biosynthesis in Leydig cells in response to LH binding onto its receptor. Bold arrows depict the Δ5 pathway preferred in the human testis. The circled numbers indicate the enzymes used by the metabolic steps: (1) cholesterol side-chain cleavage enzyme = 20,22 desmolase; (2) 17α-hydroxylase/17,20 desmolase; (3) 17β-hydroxysteroid dehydrogenase; (4) 3β-hydroxysteroid dehydrogenase; (5) aromatase; and (6) 5α-reductase. In addition, many of the steroid intermediates are sulphate-conjugated within the testis (not shown). Reproduced from Wass JAH, Stewart PM, Amiel SA, Davies MJ (2011). Oxford textbook of endocrinology and diabetes, 2nd edn. By permission of Oxford University Press.

13.6.2 Disorders of male reproduction and male hypogonadism 2391 Metabolism of testosterone Free testosterone that has diffused into tissues (e.g. prostate, scalp) may be metabolized into dihydrotestosterone (DHT) or oestradiol (E2), depending on the availability of the enzymes 5 α-reductase (Type 1: liver, skin: type 2 prostate, adrenal, seminal vesicles, genital skin, hair follicles and cerebral cortex) and aromatase respect- ively (Fig. 13.6.2.4). About 80% circulating DHT originates from tissue metabolism of T and about 20% from release from the testes. DHT and T bind to the same androgen receptor (AR), DHT having a greater than ×10 greater affinity for the AR compared to T, and therefore being the more potent. About 30 μg E2 is produced by extratesticular aromatization of testosterone and androstenedione each day, particularly in adipose tissue, bone cells and prostate, in contrast to the 10 μg secreted by the testes. Thus, T is a pro-hormone as well as a classical hormone, and its endocrine effects are both directly and indirectly mediated. Both T and DHT are catabolized in the liver by oxidation, reduction, or hydroxylation reactions, followed by conjugation with glucuronic acid or sulphation on C3 or C17. The half-life of T in the circulation is only about 10 min. The androgen receptor The androgen receptor is encoded by eight exons by a gene lo- cated near the centromere of the long arm of the X chromosome (Fig. 13.6.2.5). It is a polypeptide of 910 amino acids, with a mo- lecular weight of 98.5 kDa. It is a DNA-binding protein comprising three domains. The N terminus, encoded by Exon 1, contains a (CAGn) repeat sequence encoding glutamine repeated between 8 to 35 times. The number of repeats affects the transcriptional effi- ciency of the receptor. The greater the number of CAGn repeats, the weaker the transcriptional efficiency. It is known that the shorter the number of repeats, the greater the binding to coactivators, and therefore the greater the magnitude of the androgen effect. It is of interest that CAG repeats totalling less than 22 are associated with a greater risk of prostate cancer. A large number of repeats (>38) is associated with the androgen resistance seen in Kennedy’s syn- drome, a degenerative bulbospinal motor neuropathy. The cen-trally located hydrophilic DNA-binding domains (Exons 2 and 3) carry two zinc fingers that bind to specific DNA sequences in or next to androgen sensitive genes, and influence transcription. The carboxyterminus (exons 4–8) domains carries the hydrophobic an- drogen binding responsible for binding testosterone and DHT. Prior to androgen binding, the AR is associated with several chaperone molecules, which stabilize it. Androgen binding to AR induces a conformational change which leads to AR dissociation from these molecular chaperones (Hsp90, Hsp70, Hsp56, and immunophilins). These proteins help in maintaining the correct conformation of the receptor necessary for efficient ligand binding. Activated AR com- plexes form dimers which bind to the androgen responsive elements Table 13.6.2.1 Regulation of SHBG production Stimulation of SHBG production Inhibition of SHBG production Oestrogens (e.g. oral contraceptive pill, pregnancy) Androgen therapy Growth hormone deficiency Obesity Androgen deficiency Acromegaly Hyperthyroidism Hypothyroidism Hepatitis (especially HCV) Nephrotic syndrome Phenytoin Glucocorticoids Ageing Hyperinsulinism Antiretroviral therapies Progestogens (e.g.

danazol) X CHROMOSOME Introns: Intron size (kb): Exon size (bp): Exons:

> 26 15 26 5.6 4.8 0.8 0.7 1 2 3 4 5 6 7 8 1 2 3 4 5 6 7 4 3 2 1 p q q11–12 5 6 7 3' 5' 8 1613 152 117 288 145 131 158 155 -COOH Zn++ Zn++ Domains Transcription-regulation DNA-binding Hinge Steroid-binding NH2- GENE cDNA RECEPTOR PROTEIN Fig. 13.6.2.5 Structure of androgen receptor. The gene is made up of 8 exons, the mRNA encoding 910 amino acids. The zinc finger configuration is characteristic of all steroid hormones.

section 13 Endocrine disorders 2392 that are found in the promoter regions of androgen sensitive genes. The transcriptional activity of the androgen receptor is modulated by numerous coactivators, including SRC 1/NCoA-1, SRC2/GRIP1- TIF2 and SRC3/ACTR/AIB1, and negatively regulated by AP-1, NFκB, TR4, HBO1, and AES. A defective androgen receptor may lead to variable phenotypes of androgen insensitivity in humans. Physiological effects of testosterone The functions of T are age-related (Table 13.6.2.2). In the embryo, androgens are responsible for sexual differentiation (i.e. virilizing the external and internal genitalia). Thus, during the sexual dif- ferentiation phase, development, and growth of the Wolffian duct, epididymis, vas deferens, and seminal vesicles are pro- moted by testosterone. The enzyme 5 α-reductase, which converts T to DHT, is expressed in scrotal skin, the penile shaft, and the prostate. These tissues depend on DHT for their development (Fig. 13.6.2.6). Failure of 5 α-reductase activity leads to micropenis and incomplete/deficient labioscrotal fusion giving rise to am- biguous genitalia. At puberty, androgens, acting with growth hormone, are re- sponsible for the adolescent growth spurt, in particular for ver- tebral (i.e. upper segment) growth. It also induces promotion of secondary sexual characteristics. In adulthood, it maintains the male phenotype, sexual function as well as mediating ana- bolic effects. The endocrine (androgen synthesis) and gameto- genic (spermatogenesis) functions of the testis are interlinked. Although testosterone is important as the principal circulating androgen, its local paracrine action within the testis is crucial, together with FSH, for the initiation and maintenance of normal spermatogenesis and hence fertility. Since germ cells do not pos- sess AR, these hormones signals are transduced through the Sertoli cells and peritubular cells. Sertoli cells create an insular microenvironment in the seminiferous tubules by providing the physical framework and elaborating a chemical myriad of growth Table 13.6.2.2 Consequences of androgen deficiency before and after the onset of puberty. Hypogonadism occurring at the time of expected puberty results in a different phenotype to that acquired postpubertally Physiological action of androgen Onset of androgen deficiency before puberty Onset of androgen deficiency after puberty Increase bone mass and density Osteoporosis Osteoporosis, female fat distribution Fusion of long bone epiphyses Tall, eunuchoid habits Decrease subcutaneous/visceral fat Female fat distribution Female fat distribution Laryngeal enlargement Unbroken, high pitched voice Secondary sexual hair development Lack of pubic, axillary, and facial hair, no temporal recession Decrease facial and pubic hair, no temporal recession Increase pilosebaceous activity Lack of sebum, pale smooth skin Atrophy, fine wrinkles, pallor Stimulation of erythropoiesis Moderate anaemia Moderate anaemia Increase in muscle mass Underdeveloped, poor physical stamina Decrease strength and physical stamina Penile growth Infantile Prostate and seminal vesicle growth Underdeveloped, no ejaculate Atrophy, low volume, or absence of ejaculate Stimulation of spermatogenesis Not initiated, very

small testes Regression, small testes Stimulation of sexual interest Not developed Decrease Stimulation of erectile function Low/absent spontaneous erection Decrease erection Effect on mood and behaviour Placid Low moods, unassertiveness, tiredness 5-α reductase Aromatase Sexual differentiation Secondary sexual hair growth Production of sebum Prostatic growth Sexual differentiation Muscle growth Increase in bone mass Erythropoiesis Erythropoietin synthesis Sexual potency and libido Psychotropic effects Dihydrotestosterone Oestradiol Bone mass Epiphyseal fusion Psychotropic effects Negative feedback modulation of gonadotrophin secretion Prostate growth (complex effects) TESTOSTERONE Fig. 13.6.2.6 Testosterone is metabolized to dihydrotestosterone by the enzyme 5-α reductase and to oestradiol via the aromatase enzyme. These hormones exert different effects to testosterone.

13.6.2 Disorders of male reproduction and male hypogonadism 2393 factors and cytokines for the developing germ cells. Sertoli cells also secrete inhibin B, a glycoprotein hormone which inhibits FSH secretion by the pituitary. Male hypogonadism Male hypogonadism is a descriptive term for the clinical complex associated with androgen deficiency due to failure of Leydig

cell function. Concomitant impairment of spermatogenesis is likely since the seminiferous tubules will also be androgen deficient or directly involved by the same pathological process. However, infertility is usually an isolated abnormality of spermatogenesis where patients seldom show any clinical of androgen deficiency. In the past several years, an increasing number of specific genetic defects have been identified by genomic DNA mapping to be asso- ciated with abnormal gonadal function

and development. New light has been shed on the pathogenesis of these conditions. Aetiologies There are a large number of pathological conditions that can lead to de-struction or malfunction of the hypothalamo-pituitary-testicular axis (Tables 13.6.2.3 and 13.6.2.4). It is important to identify the underlying cause of hypogonadism and distinguish between pituitary/ hypothalamic Table 13.6.2.3 Classification and aetiologies of male reproductive disorders Site of lesion Clinical picture Androgen deficiency

Infertility Hypothalamus and pituitary (hypogonadotropic hypogonadism) Isolated GnRH deficiency Congenital GnRH deficiency + + Kallmann syndrome Anosmia and GnRH deficiency + + GnRH insensitivity GnRH receptor gene mutation + + Fertile eunuch (Pasqualini syndrome) Partial GnRH deficiency, low LH +

Hypogonadotropic hypogonadism/adrenal hypoplasia DAX-1 gene mutation + + Constitutional delayed puberty Self-limiting + + Male anorexia nervosa Weight-related, reversible GnRH deficiency + + Hyperprolactinaemia Pituitary tumour, drug induced + + Congenital hypopituitarism PROP 1 gene mutation, hypogonadotropic hypogonadism prolactin, GH, ACTH deficiencies + + Acquired hypopituitarism Pituitary tumour, craniopharyngioma, haemachromatosis irradiation, hypophysitis, transfusion haemosiderosis, sarcoidosis, tuberculosis, histiocytosis X + + Biologically inactive LH LH β gene mutation + + Isolated FSH deficiency FSH β gene mutation ? + Testicular (hypergonadotropic hypogonadism) Klinefelter’s syndrome 47XXY, 48XXXY,47XXY/46XY mosaic, and so on + + 46XX male SRY gene translocation to X chromosome + + Sex chromosome/autosomal abnormalities Translocation, deletion + – Mixed gonadal dysgenesis XY/XO, true hermaphroditism + + Testicular agenesis Absence of testes postnasally + + Testicular torsion Destruction of testicular tissue + + Surgical orchidectomy, testicular trauma, tumour orchitis Destruction of testicular tissue + + Sickle cell disease Microinfarcts of the testes + + Noonan–Leopard syndrome 12q22 gene defect, autosomal-dominant cryptorchidism, Turner’s stigmata, with short stature, webbed neck, pectus excavatum hypertelorism, ptosis, right sided congenital heart disease Persistent Müllerian duct syndrome AMH gene or AMR receptor type II gene mutation, Fallopian tube, and uterus present with cryptorchidism +/- + Congenital

steroidogenic enzyme deficiencies 10q.24.3 CYP17 17,20-desmolase, 9q22 HDD17b3, 17OH-steroid DH gene mutation + + (continued)

section 13 Endocrine disorders 2394 Site of lesion Clinical picture Androgen deficiency Infertility LH insensitivity LH receptor mutation, pseudohermaphroditism + + Idiopathic infertility Defective spermatogenesis of uncertain aetiology – + Varicocele Reflux in spermatic vein – + Microdeletions Yq Deletion of azoospermic factor – + Cryptorchidism Congenital deficiency of testosterone or AMH action, dysgenetic gonads +/– + Immotile cilia syndrome Absent dynein arms of sperm tail microtubules – + Globozoospermia Absence of acrosome cap on sperm head – + FSH insensitivity 2q21 FSH receptor gene mutation ? + Post-testicular Immunological Sperm antibodies – + Immotile cilia Dynein arms absent in sperm tail – + Young's syndrome Mercury poisoning? – + Congenital bilateral absence of vas deferens CFTR gene mutation and intronic variant – + Genital tract infection Postinfection, postvasectomy, herniorrhaphy – + Accessory gland/prostate infection Bacterial, chlamydia, abnormal seminal fluid – + Retrograde ejaculation Autonomic neuropathy, postprostatectomy – + Coital insufficiency Defective vaginal insemination – + Target tissues Androgen insensitivity syndromes Xq11-12 androgen receptor gene mutation + + Androgen receptor defects Xq11-12 androgen receptor gene CAG repeat expansion + + 5-α reductase deficiency 2p23 5 α reductase 2 gene mutation + + Oestrogen insensitivity ER α gene mutation – ? Aromatase CYP19 gene mutation – ? Systemic diseases Acute critical illness Cytokine or cortisol-induced multilevel dysfunction + – Chronic illness: congestive cardiac failure, neoplasia, uncontrolled diabetes mellitus Cytokine or caloric deprivation induced multilevel dysfunction in HPT axis + + Liver cirrhosis Primary testicular failure, followed by gonadotrophin deficiency + + Chronic renal failure Hypogonadotropic hypogonadism + + Thyrotoxicosis Increased SHBG, gonadotrophins, oestradiol + + Cushing's syndrome Multilevel dysfunction in HPT axis + + Haemochromatosis Hypogonadotropic + + HIV infection Hypogonadotropic + + Morbid obesity Hypogonadotropic, low SHBG, total, free T + + Obstructive sleep apnoea Hypogonadotropic + + Rheumatoid arthritis Suppression of testosterone during flare up + ? Acute febrile illness Temporary suppression of spermatogenesis – + Untreated congenital adrenal hyperplasia Suppression of gonadotrophin – + Neurological diseases Dystrophia Myotonin protein kinase (MT-PK) gene CTG repeat expansion + + Prader–Willi syndrome Deletion/mutation of imprinting centre in paternal 15q11-13, hypogonadotropic, mental retardation hypotonia, hyperphagia, obesity, short stature + + Laurence–Moon syndrome Hypogonadotropic, retinitis pigmentosa, mental retardation, obesity, polydactyly + + Table 13.6.2.3 Continued

13.6.2 Disorders of male reproduction and male hypogonadism 2395 (secondary or hypogonadotropic hypogonadism), and testicular (pri- mary or hypergonadotropic hypogonadism) disorders. The causal lesion may require specific treatment (e.g. as in the case of a prolactin se-creting pituitary tumour and haemochromatosis). Hypogonadotropic conditions are amenable to treatment aimed at inducing or restoring spermatogenesis, while in primary testicular failure—which is usually irreversible—only testosterone replacement therapy is possible.
Clinical features General clinical features of hypogonadism The age of onset of androgen deficiency critically influences the manifestations of hypogonadism (Table 13.6.2.2). Prepubertal onset of testosterone deficiency gives rise to sexual infantilism and patients present with delayed puberty. Eunuchoid body proportions (arm span greater than height and heel to pubis exceeding crown to pubis lengths by at least 5 cm) develop due to the continued growth of long bones (growth hormone mediated, allowed by the delayed closure of epiphyses due to lack of

testosterone/oestradiol-induced spinal growth in late puberty). Postpubertal onset of testosterone deficiency leads to regression of spermatogenesis, low libido, erectile malfunction, loss of ejaculation, sarcopenia, poor stamina, and decreased secondary sexual hair and shaving frequency. However, no change is observed in body and penile proportions nor voice. Symptoms and signs of hypogonadism usually develop and progress insidiously. It is therefore common for patients to present many years following the onset of hypogonadism. Furthermore, younger patients who have never been adequately an- drogenized may not be aware, or even deny, that sexual function is subnormal. By contrast, after surgical or traumatic/inflammatory cas- tration, adults may experience hot flushes from acute withdrawal of androgens. Fetal onset of defective androgen action due to androgen receptor abnormalities or defects of steroidogenic enzymes, will cause failure of masculinization of the genitalia resulting in intersexual states. Clinical findings associated with hypogonadism Hypothalamo-pituitary tumours should be considered in the pres- ence of headache, defects of visual acuity or visual field loss, polyuria and polydipsia suggesting diabetes insipidus, or clinical /biochemical Site of lesion Clinical picture Androgen deficiency Infertility Bardet–Biedl syndrome Defects in BBS loci 16q11, 15q23.3, or 3p12 hypogonadotropic, retinitis pigmentosa, mental retardation, polydactyly + + Familial spinocerebellar degeneration 9p frataxin gene GAA repeat expansion, hypogonadotropic, progressive ataxia + + Kennedy syndrome X911-12 androgen receptor gene CAG repeats expansion, late-onset androgen resistance, progressive spinobulbar muscular atrophy + + Temporal lobe epilepsy Unknown + – Spinal cord injury Abnormal thermoregulation or neuroregulation of testes – + Fragile X syndrome FMR 1 gene CCG repeats expansion, mental retardation, macro-orchidism – – Drugs/chemical or physical agents Digitalis, spironolactone, cyproterone acetate, flutamide, bicalutamide, cimetidine Antiandrogenic + + Corticosteroids Multilevel dysfunction in HPT axis + + Ketoconazole Inhibits steroidogenesis + + Aminoglutethimide Antipsychotics, sedatives Hyperprolactinaemia, gonadotrophin suppression + + Anticonvulsants Increase SHBG, decreased free testosterone + + Ethanol Direct suppression of testicular function, hepatotoxic + + Opiate, cocaine, cannabis abuse Suppression of gonadotrophin + + Cytotoxic drug Agent specific, dose-related germ cell loss – + Ionizing radiation Dose-dependent loss of spermatogenesis, spermatocytes – + Sulfasalazine Abnormal sperm morphology and motility – + Nitrofurantoin Direct suppression or antiandrogenic – + Anabolic steroids, oestrogens, progestins Gonadotrophin suppression or antiandrogenic (+) + Lead, mercury, cadmium Adverse effects on spermatogenesis – + Pesticides, fungicides, amoebicides Direct toxic effects on spermatogonia – + HPT, hypothalamic–pituitary–thyroid axis. Table 13.6.2.3 Continued

 evidence of pituitary hormone excess such as that found in Cushing’s disease, acromegaly, and hyperprolactinaemia. Hyperprolactinaemia causes loss of libido even in the presence of apparently normal tes- tosterone concentrations. Primary testicular failure is suggested by a history of orchitis, torsion, testicular trauma, surgery, chemotherapy, irradiation. An increasing number of chronic systemic diseases (Table 13.6.2.3) are associated with compromised hypothalamo- pituitary-testicular function. With improved survival resulting from specific treatments, the role of gonadal dysfunction in the quality of life of these patients is becoming increasingly recognized. A history of excess alcohol consumption, use of recreational drugs and consumption of medications that interfere with pituitary- testicular function or androgen action should be specifically eluci- dated. Ethanol causes a lowering of plasma testosterone through a direct toxic effect on Leydig cell steroidogenesis. Testicular atrophy and gynaecomastia, found in 50% of men with liver cirrhosis, are due to disordered androgen steroid metabolism, an increase in sex hormone binding globulin, coupled with an increased oestrogen production. These

changes are usually irreversible. Neurological diseases can be associated with hypogonadism. Postpubertal atrophy of the seminiferous tubules occurs in 80% of patients with dystrophia myotonica, an autosomal-dominant disorder characterized by myotonia, distal muscle atrophy, lens opacification, and premature frontal balding. Variable degrees of androgen deficiency also coexist. Hypogonadotropic hypogonadism is associated with familial cerebellar ataxia, Gordon Holmes ataxia, Lawrence Moon, Bardet–Biedl, and Prader–Willi syndromes. Defective spermatogenesis is common in paraplegia or quadriplegia following spinal cord injury, perhaps due to the inability to maintain a low scrotal temperature. Specific conditions Primary gonadal failure Klinefelter's syndrome Klinefelter's syndrome is the commonest cause of male hypo- gonadism with an incidence of 2 per 1000 live births. It is a devel- opmental disorder of the testes resulting from the presence of an Table 13.6.2.4 Phenotypic characteristics associated with genes that cause hypogonadotropic hypogonadism (HH) Gene Gene product Inheritance Clinical phenotype GnRH GnRH Autosomal recessive Normosmic HH GnRHR Gonadotrophin releasing hormone receptor Autosomal recessive Normosmic HH LH β Luteinizing hormone β chain Autosomal recessive Normosmic HH SEMA3A Semaphorin-3A Autosomal dominant IHH and anosmia SOX10 SOX10 Autosomal dominant IHH and anosmia, Waardenburg syndrome NR0B1 DAX-1 X-linked X-linked adrenal hypoplasia and HH KAL-1 Anosmin-1 X-linked IHH and anosmia, synkinesis, solitary kidney FGFR1 FGF receptor 1 Autosomal dominant Normosmic HH, craniofacial defects, digital anomalies of toes, dental agenesis FGF8 Fibroblast factor 8 Autosomal dominant Normosmic HH FGF17 Fibroblast growth factor 17 Single allelic defect insufficient Normosmic HH HS6ST1 Heparan-sulphate 6-0-sulphotransferase Nonmendelian HH +/- anosmia IL17RD Interleukin 17 receptor D Single allelic defect insufficiency IHH and anosmia, hearing loss DUSP6 Dual-specific phosphatase 6 Single allelic defect insufficient HH SPRY4 Sprouty homologue 4 Single allelic defect insufficient HH FLTR3 Fibronectin leucine-rich transmembrane protein 3 Single allelic defect insufficient HH NELF Nasal embryonic LHRH factor Single allelic defect insufficient HH+/- anosmia CHD7 Chromodomain helicase DNA-binding protein-7 Autosomal dominant HH+/-anosmia, CHARGE syndrome PROK2 Ligand for G protein coupled prokinecitin receptor-2 Heterozygous mutations, oligogenic inheritance HH +/- anosmia PROKR2 G-protein-coupled prokineticin receptor-2 Heterozygous mutations, oligogenic inheritance HH +/- anosmia WRD11 WD repeat containing protein-2 Heterozygous missense mutations HH+/- anosmia GPR54 KISS1-derived peptide receptor Recessive mutations HH KISS1 Metastin or kisspeptin Recessive mutations HH TACR3 Neurokinin B receptor Recessive mutations HH TAC3 Neurokinin B Recessive mutations HH LEP Leptin Recessive mutations HH LEPR Leptin receptor Recessive mutations HH IHH, 'isolated' or 'idiopathic' HH; LHRH, luteinizing hormone-releasing hormone.

 additional X chromosome derived from nondisjunction of parental (maternal origin in two-thirds of cases) germ cells during meiosis. In fewer than 5% of patients, the nondisjunction occurs during mi- tosis of the zygote. Such postfertilization mitotic nondisjunction will result in mosaicism. The most common karyotype is 47XXY (80 to 90%), but rarer variants include 46XY/47XXY mosaic, mul- tiple X+Y, and the so-called XX male syndrome. Unlike many other numeral aberrations of chromosomes, KS is not associated with an increased rate of miscarriage. The risk of having a child with KS increases with both increasing maternal and paternal age. The signs of Klinefelter's syndrome are almost unnoticeable in childhood. Accelerated atrophy of germ cells before puberty and hyalinization of the seminiferous tubules give rise to very few intact gametes, and the usual outcome is sterility and small firm (around 4 ml) testes. Individual tubules with intact spermatogenesis are seen in

patients with the mosaic form 46,XY/47,XXY and very occasion- ally motile sperms are found in the semen. Leydig cells appear rela- tively hyperplastic, although Leydig cell mass is in fact normal. The degree and impact of the Leydig cell steroidogenic defect (of uncer- tain aetiology) is very variable, ranging from the virilized adult male presenting with infertility, to the eunuchoid youth who fails to com- plete sexual maturation. In KS, the extra X chromosome carrying the androgen receptor with a short CAG repeat length in Exon 1 (i.e. greater AR activity) undergoes activation preferentially. Thus, the skewed inactivation of the X chromosome resulting in the preferen- tial activity of the long CAG repeat may contribute to the phenotypic severity and variability of KS. In adults, libido and potency are ini- tially normal, but decrease between the ages of 25 and 35, reflecting an increasing insufficiency of Leydig cells. In mid-adulthood, 80% of patients have reduced testosterone with elevated LH/FSH and oes- tradiol levels. Other clinical features include gynaecomastia, reduced body hair, long legs, tall stature (eunuchoid proportions), and learning (verbal and cognitive) difficulties, poor school performance, behavioural disturbances, and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome, as well as type 2 diabetes mellitus. Infants with KS may manifest with micropenis, hypospadias, cryptorchidism, or developmental delay. In addition to relatively tall stature, some patients have clinodactyly, hypertelorism, elbow dysplasia, high arched palate, hypotonia, lan- guage delay or reading and learning disabilities requiring therapy occurs in up to 70%. Character and personality disorders and be- havioural problems occur commonly, possibly in part because of the psychosocial consequences of androgen deficiency. IQ scores may be reduced by 10–15%, though not into the intellectual disability range. There is also an increased incidence of osteopenia, mitral valve prolapse, breast tumours (3–5%: the risk increases if there is a family history of breast cancer among female relatives), testicular and extratesticular germ-cell tumours (especially mediastinal and retroperitoneal), varicose veins, and leg ulcers. Taurodontism, char- acterized by enlarged molar teeth resulting from enlargement and ex- tension of the pulp chamber, is present in 40% of men with KS. Mental retardation is associated with higher order X chromosome polysomy. Diagnosis and laboratory findings Testicular volumes of less than 4 ml should always lead to a suspicion of KS. Serum testos- terone (T) is often reduced or lies in the lower reference range (40% patients), and free T is more frequently reduced than total T as the SHBG level tends to be increased. As LH stimulation is increased, Leydig cells produce relatively more oestradiol, with increase in free E2 to free T ratios. The Barr chromatin body test is a rapid investi- gation used to determine a chromosomal abnormality in a swab of cheek mucosa, but the definitive diagnosis rests on karyotyping of lymphocytes. Therapy Androgen deficiency, as evidenced by a rise in LH, should prompt replacement therapy with testosterone. Androgen treatment should start early in the adolescent as this significantly promotes psychosocial development, and may prevent the development of gy- naecomastia and reduce the risk of breast cancer. It is important also for adequate development of secondary sexual characteristics, at- tainment of peak bone mass and bone mineral density and strength, energy, motivation, mood, and behaviour. If gynaecomastia is cos- metically unacceptable, mastectomy may be indicated. Infants with micropenis may benefit from topical testosterone, and early inter- vention with speech and language therapy is important if speech delay and dyslexia are present. Dystrophia myotonica This is an autosomal-dominant inherited condition, characterized by delayed muscle relaxation after contraction, dystrophy of the distal musculature and pharyngeal muscles, cataracts, hyperacusis, and frontotemporal hair loss. 80% of affected males develop a pro- gressive untreatable primary hypogonadism with testosterone defi- ciency and damage to the germinal epithelium, with accompanying reduced testicular volumes, and hyalinization of the seminiferous tubules and vacuolation of Sertoli cells.

60% of affected males have testosterone deficiency, with loss of libido and impotence. Gonadotrophins are increased, particularly FSH. Tuberculosis Tuberculous orchitis is rare, but should be included in the differ- ential diagnosis of testicular tumours. The scrotal mass is usu- ally painless, and haematospermia, sterile pyuria, hydrocele, and oligoasthenoteratozoospermia may be present. Leprosy This can cause a granulomatous infiltration of the testes and up to 60% of affected males are hypogonadal, particularly with lep- romatous leprosy, though rarely with the tuberculoid form. Gynaecomastia may be present, and testosterone levels are low with increased gonadotrophin. Transverse section of the spinal cord Severe trauma to the spinal cord often leads to exocrine testicular insufficiency. Testosterone secretion often returns to normal spon- taneously, but spermatogenesis is usually permanently impaired in paraplegics and tetraplegics. This is thought to occur as a conse- quence of disorders of thermoregulation and circulation. Secondary gonadal failure This can result from absent or defective GnRH secretion, or failure of the anterior pituitary to respond to GnRH released from the me- dian eminence, leading to hypogonadotropic hypogonadism (HH). Kallmann syndrome and other forms of inherited HH This has an incidence of 1 in 7500 males, and is a sporadic or familial (X-linked or autosomal) form of congenital hypogonadotropic

 hypogonadism associated with several somatic congenital abnor- malities including anosmia or hyposmia (defective smell sense), hereditary bimanual synkinesis (mirror hand movements), nerve deafness, cleft lip or palate, renal malformations, and dental abnormalities. There are now over 20 genes whose mutations have been in- criminated in the pathogenesis of congenital hypogonadotropic hypogonadism. One of the most severe phenotypes is seen in X-linked Kallmann syndrome, caused by mutations or deletions within the KAL-1 gene, located in the Xp22.3 region, encoding the cell adhesion protein anosmin-1. This is associated with faulty embryonic migration of GnRH secreting neurons from their site of origin in the medial olfactory placode into the hypo- thalamus, thereby preventing normal neurosecretion of GnRH (gonadotrophin releasing hormone) into the median eminence capillary circulation such that it does not reach the gonadotrophs of the anterior pituitary, resulting in hypogonadotropic hypo- gonadism. Associated maldevelopment of the olfactory bulb is responsible for anosmia. Patients present with delayed puberty, but the diagnosis may be suspected when neonatal males have undescended testes. Several additional genes are mutated in Kallmann syndrome that affect the fate and migration of GnRH neurons. Some of these will be associated with ‘isolated’ or ‘idiopathic’ hypogonadotropic hypogonadism (IHH) and anosmia, while others are associated with IHH alone (normosmic forms of IHH) (Table 13.6.2.4). Genes encoding fibroblast growth factor 8 (FGF8) signalling pathway proteins, chromodomain helicase DNA-binding protein 7 (CHD7) and sex determining region Y-Box 10 (SOX10) affect the neurogenic niche in the nasal area and craniofacial development. Prokineticin-2 and prokineticin receptor 2 (encoded by PROK2 and PROKR2, respectively), WD repeat domain 11 (encoded by WDR11), semaphorin 3A (encoded by SEMA3A) and FEZ family zinc finger 1 (encoded by FEZF1) influence the migration of GnRH neurons. Postmigratory GnRH neurons are embedded in a complex neur- onal network of afferents that send information about permis- sive reproductive cues such as steroid and metabolic hormones to these cells (Fig. 13.6.2.2). Individual components of the underlying neural circuits are increasingly recognized, and some key molecules have been discovered through the study of the genetics of isolated hypogonadotropic hypogonadism. Inactivating mutations in genes encoding kisspeptin-1 (KISS1) and its receptor (KISS1R) arrest pubertal development in humans. Extensive experimental studies in various species have demonstrated that kisspeptin-producing neurons are major

afferents to GnRH neurons and essential for dif- ferent aspects of GnRH function, ranging from the tonic feedback control of GnRH and/or gonadotropin secretion to generation of the preovulatory surge responsible for ovulation. Although kisspeptins are not essential for GnRH neuron migration, experimental data has documented that populations of kisspeptin neurons undergo a dynamic process of prenatal and postnatal maturation enabling them to establish connections with GnRH neurons early in devel- opment (under the control of steroid hormones). Similarly, identi- fication of mutations in TAC3 (encoding tachykinin-3, cleaved to form neurokinin B) and TACR3 (encoding tachykinin receptor 3; also known as neuromedin-K receptor or NKR) in patients with IHH have underlined the importance of the tachykinin family in the control of GnRH neurons. These findings led to the identification of a subpopulation of afferent neurons in the arcuate and/or infundibular hypothalamic region, coexpressing kisspeptins and neurokinin B (NKB), and it appears that the actual number of kisspeptin and/or NKB neurons change during development. Mutations in proteins that regulate ubiquitination such as OTU domain-containing pro- tein 4 (encoded by OTUD4) and E3 ubiquitin-protein ligase RNF216 (also known as ring finger protein 216; encoded by RNF216), as well as in proteins involved in lipid metabolism such as neuropathy target esterase (also known as patatin-like phospholipase domain- containing protein 6; encoded by PNPLA6), have been identified in patients with Gordon Holmes syndrome (with associated IHH and ataxia). Thus, mutations in these three genes give rise to a broad and progressive neurodegenerative syndrome that includes IHH. Haploinsufficiency of DMXL2, which encodes synaptic pro- tein DmX-like protein 2, has been shown to cause a complex new syndrome associating IHH with polyendocrine deficiencies and polyneuropathies. Peripheral signals that convey information about metabolic status indirectly modulate GnRH neurosecretion as evidenced by the reproductive phenotype of absent pubertal development and hypogonadotropic hypogonadism in patients with inactivating mu- tations in the genes encoding leptin (LEP) or its receptor (LEPR). Experimental data suggest that kisspeptin neurons are sensitive to changes in leptin concentrations and metabolic conditions by an in- direct mechanism. Mutations of the GnRH locus and in the GnRH receptor cause IHH with normal olfactory function. This also occurs in patients with LH β-gene mutations (Table 13.6.2.4). Oligogenicity and reversibility in IHH Recent evidence suggests that in a few cases the coexistence of mutations in several genes incriminated in IHH may be necessary for full phenotypic expres- sion. This may explain why phenotypic penetrance can be variable with an identical genotype at one locus shared by several members of a kindred. It has also been shown that the HH phenotype is po- tentially reversible in up to 10% of patients with IHH. Late-onset hypogonadism Total and free testosterone decline gradually and in varying degrees in men from the age of 40 onwards. This is amplified by the age- related increase in SHBG levels exacerbated by concomitant sys- temic diseases and the use of some medications. Differentiation of nonspecific symptoms of ageing such as frailty, decreased muscle strength, lack of stamina and vitality, decline in libido, from those of mild classical hypogonadism can be difficult. A significant percentage of men over 60 years of age have serum testosterone levels below the lower limits of normal for young male adults (20 to 30 years), and some longitudinal studies have suggested that as many as 20% of men in their 60s and approximately 50% of men in their 80s have serum total testosterone (TT) levels signifi- cantly below those of normal young men. However, the European Male Ageing Study (EMAS) estimated a much lower prevalence (2.1%) of symptomatic late-onset hypogonadism in the popula- tion. It is evident that the clinical symptoms/manifestations in this age group may be more difficult to recognize because of masking by comorbid illnesses. There is controversy as to the significance of falling testosterone levels with age, some believing that it is a

13.6.2 Disorders of male reproduction and male hypogonadism 2399 medically significant condition resulting in significant detriment to the quality of life and adversely affecting the function of multiple organ systems, while others suggest that it is a chemical marker of generalized illness. Although significant advances have been made in improving the understanding of the pathophysiology of the hypogonadism, the diagnostic methods used to diagnose low testosterone levels, and testosterone replacement therapy, a great deal of confusion and mis- understanding still exists among clinicians and patients about the diagnosis of hypogonadism in ageing men, and benefits and risks associated with testosterone therapy. The important questions as yet unanswered questions are: (1) How to diagnose late-onset hypo- gonadism in ageing males? (2) What are the best treatment options for late-onset hypogonadism? (3) Will older hypogonadal men benefit from testosterone treatment? (4) What are the risks associ- ated with such interventions? Investigation Confirmation of hypogonadism The clinical suspicion or diagnosis of hypogonadism must be con- firmed by demonstration of low circulating testosterone before re- placement therapy can be envisaged. It is recommended that blood samples be obtained between 8 to 9 AM, avoiding the circadian fall in levels of testosterone seen later in the day. The interpretation of total testosterone requires measurements of SHBG, which can alter in ageing, obesity, with the use of anticonvulsive medications, dia- betes, iron overload, and liver disease. The free testosterone can be calculated from the total testosterone, SHBG and albumin concen- trations using the Vermeulen formula (see http://www.issam.ch/ freetesto.htm for calculator). Assessment of the hypothalamo-pituitary-testicular axis and the target tissue androgen resistance Measurement of LH, FSH, and testosterone are required to dis- tinguish between primary and secondary hypogonadism. In primary gonadal failure, LH and FSH levels are elevated and testosterone levels low, whereas in secondary gonadal failure low testosterone levels are associated with inappropriately low gonadotrophins. Causes of hypo and hypergonadotropic hypo- gonadism are listed in Table 13.6.2.3, as are other conditions that can impair fertility. Pathologies in the hypothalamus and pituitary give rise to low or low normal gonadotrophins and low testosterone (hypogonadotropic hypogonadism or secondary testicular failure), where the potential for stimulating testicular function by exogenous gonadotrophin or GnRH replacement is maintained. Conditions affecting the testes will interrupt normal testicular negative feedback. This results in elevated gonadotrophin levels with a low testosterone, characteristics of a hypergonadotropic hypogonadal state (primary testicular failure). Failure of spermatogenesis with reduced testicular size is commonly associated with a rise in FSH alone. The value of es- timation of circulating inhibin B and Müllerian inhibiting hor- mone (MIH) for diagnostic purposes is currently being assessed. Patients with androgen insensitivity syndromes have elevated testosterone with high LH, but normal to low FSH. Increased LH or FSH is associated with a very rare LH and FSH resistance syndromes. Human chorionic gonadotropin (HCG) stimulates Leydig cell steroidogenesis and increases plasma testosterone level over 4 to 7 days. Administration of HCG is useful for detecting the presence of functional testicular tissue in patients with impalpable testes, and to assess functional reserve of the testes prior to treatment with exogenous gonadotrophin or GnRH, and in differentiating hypergonadotropic hypogonadism from rare causes who produce immunologically detectable but biologically inactive LH excess. Stimulation tests of gonadotrophin secretory reserve using clomi- phene and GnRH seldom give additional information and have be- come largely obsolete, especially with the improved sensitivity and range of modern gonadotrophin assays. Assessment of the pituitary Patients with hypogonadotropic hypogonadism without the stigmata of Kallmann syndrome should undergo full anterior pitu- itary functional evaluation and an anatomical basis sought for their gonadotrophin deficiency (e.g. a mass lesion in the hypothalamo-

pituitary region). They require pharmacological tests of growth hormone and ACTH reserve, thyroid function tests, visual field charting, and MR or CT scanning of the hypothalamus-pituitary region. Other investigations Ultrasound and MR scanning are useful in locating ectopic or intra- abdominal testes. DNA analysis can help confirm the diagnosis of androgen resistant syndromes and an increasing number of rare causes of hypogonadism such as haemochromatosis.
Treatment objectives The treatment objectives are to: 1. Relieve the symptoms of androgen deficiency 2. Prevent the long-term consequences of androgen deficiency such as osteopenia 3. Reproduce physiological circulating and tissue levels of plasma testosterone, dihydrotestosterone, and oestradiol 4. Induce fertility if required in hypogonadotropic patients 5. Treat any specific underlying disorder The mainstay of treatment of the hypogonadal male is androgen re- placement therapy. Although hypogonadotropic patients have the potential for fertility, gonadotrophin and pulsatile GnRH therapy should only be employed where there is a requirement for fertility because of the expense and complexity of these regimens. Previous testosterone exposure does not jeopardize response to gonado- trophins, hence younger hypogonadal subjects should be treated by testosterone in the same manner as hypergonadotropic patients to initiate and maintain virilization and sexual function. Modalities of androgen replacement therapy The circulating half-life of free testosterone is around 10 minutes due to rapid metabolism by the liver. To achieve sustained physio- logical circulating concentrations, testosterone must be adminis- tered in a modified form or by a parenteral route so that its rate of metabolism or absorption is retarded. Injectable testosterone esters are the commonest first-line an- drogen preparations. A mixture of four different testosterone

 esters (propionate, phenylpropionate, isocaproate, and decanoate) (Sustanon, 250 mg 2 to 3 weekly) and testosterone enanthate (Primoteston Depot) are the most popular. While undoubt- edly effective, these preparations inevitably give rise to high supraphysiological peak testosterone levels within the first week, which then fall sharply to the lower limit of normal before the next dose. Some patients are disturbed by fluctuations in libido, mood and stamina associated with the repeated rise and fall of testosterone levels, as well as by the painful deep intramuscular injections. Crystalline testosterone compressed into cylindrical palates, surgically implanted subcutaneously under local anaesthesia, pro- vide a depot source of testosterone which last 6 to 8 months. Peak testosterone levels are achieved after 2 to 4 weeks followed by a gradual decline over the subsequent months. A total dose of 800 mg can maintain physiological concentrations of testosterone for between 6 to 8 months, which some patients find more convenient than more frequent injections. The implantation procedure can be conducted as an outpatient, although rarely can be complicated by haemorrhage or infection, and in inexperienced hands 10% of im- planted pellets may be extruded, often quite late. Implants should only be used as maintenance therapy in patients who have already shown satisfactory tolerance to the androgen effects of shorter acting preparations. Testosterone undecanoate is administered orally, but low bio- availability (<0.5%), variable absorption, the requirement for mul- tiple daily dosing, and higher costs, have restricted its use despite the obvious appeal of oral administration. To maintain testosterone consistently within the physiological range, two to three times daily administration of 80 mg of testosterone undecanoate is required. Moreover, intestinal 5 α-reductase activity gives rise to a dispropor- tionate and unphysiological increase in dihydrotestosterone relative to testosterone. Oral testosterone undecanoate is useful in the in- duction of puberty in adolescence, where lower doses are preferable, and as second line treatment in adults who are intolerant of injec- tions or implants. 17 α-alkylated androgens are relatively

weak androgens, but some may have more potent anabolic effects. 17 α-alkylated compounds cause cholestatic jaundice in a reversal and dose-related manner, while long-term treatment has been associated with peliosis hepatis (haemorrhagic cysts) in the liver, and rarely with liver adenomas or tumours. Consequently, 17 α-methyl testosterone, oxymetholone, fluoxymesterone have now been withdrawn from the market in several countries. As a group, 17 α-alkylated androgens are not re- commended for clinical use, but they remain commonly abused as anabolic steroids. Mesterolone, which is not hepatotoxic, is a weak androgen with low clinical efficacy and remains commercially available. Transdermal testosterone preparations offer stable physiological levels of testosterone without peaks and troughs, painless self ad- ministration, and minimal risks of overdose and low potential for abuse. Testogel (50 mg), Testoderm (50 mg), and Tostran gel (50 mg) are three transcutaneous preparations available in the United Kingdom. These gel preparations have a bioavailability of around 10% and deliver 5 mg or so into the body (equivalent to the daily testosterone production rate of the testes). They are applied to the skin in the shoulder or central abdominal areas, and increase serum testosterone levels into the normal range within one hour of application. Steady state levels are achieved 48–72 hours after initiation of therapy. The gels have a low incidence of skin irrita- tion, ease of application, invisibility of the dried gel, and have the ability to deliver testosterone dose-dependently to the low, mid, or upper normal range. Passive transfer of applied testosterone to women and children can be avoided by covering the skin by clothing or showering 6 hours after application. The gels should not be applied to the genitalia and breast area. The choice of preparation depends on age of the patient, the patient's own preference, facilities for injections, and available ex- pertise for surgical implants. Many boys with constitutional delayed puberty will spontaneously enter or progress into puberty after a short course of testosterone, for example intramuscular testos- terone enanthate 50 mg monthly or oral testosterone undecanoate 40 mg daily for 3 to 6 months. The low doses of testosterone will stimulate linear growth and promote virilization without prema- ture epiphyseal fusion. In patients with no evidence of spontan- eous progression, gradually increasing doses of testosterone over 3 to 4 years will ensure full virilization, except for testicular growth. They can be maintained on adult replacement doses subsequently if hypogonadotropic hypogonadism appears to be permanent. Treatment can be safely started after the age of 14. Indeed, de- layed treatment can be associated with permanently impaired peak bone mass. The invasive nature of the implantation procedure and the long duration of action makes implants less than ideal for the induc- tion of puberty in adolescence and the initiation of treatment in androgen—naive young adults, where a more gradual and flexible increase in dose is desirable. For these reasons, implants are usually reserved for maintenance treatments in young adults, replacement therapy having been initiated with intramuscular or oral transcu- taneous preparations. Almost all adult patients respond well to testosterone enanthate 200 mg (2-weekly), 300 mg (weekly), or Sustanon 250 mg (2–3 weekly). In the absence of a satisfactory biological marker for androgen action, monitoring of treatment is best gauged by clinical response and documenting that plasma testosterone is in the low–normal range immediately before the next dose, so that appropriate adjustments of dosing intervals can be made. Hypogonadal patients over the age of 50 starting testosterone treatment for the first time should be checked for pre-existing occult prostatic cancer with the digital rectal examination and prostate- specific antigen (PSA) estimation, and these should be repeated in the first 3 to 6 months after initiating treatment to ensure there is no significant change. Subsequent monitoring for prostatic disease should not differ from eugonadal men of comparable age since there is no increased relative risk in hypogonadal patients on long-term testosterone. Testosterone replacement therapy is safe and side effects are rare, although these may include acne, transient

priapism, gynae- comastia, fluid retention, increasing haematocrit, obstructive sleep apnoea, and exacerbation of existing behavioural disturbances. Testosterone is contraindicated in patients with known prostatic or breast cancer. In older patients with benign prostatic hyperplasia, sleep apnoea, polycythaemia, dyslipidaemia, cardiac failure, liver disease, or renal failure, a cautious approach with reduced doses of testosterone, careful dose titration, and close supervision or specific management of the coexisting problems, usually allow patients to benefit from androgen replacement.

13.6.2 Disorders of male reproduction and male hypogonadism 2401 Infertility Infertility is defined as the inability of a couple to initiate a preg- nancy after 12 months unprotected intercourse. It is estimated that 8 to 15% of couples experience involuntary infertility. Of these, male factors alone are estimated to be responsible in up to 30%, and contributory in a further 20% of subfertile couples. Thus, male in- fertility may affect 5% of men of reproductive age. A secular trend of declining semen quality (sperm density) in men over the last 50 years has been reported in some but not other regions of Europe. This, together with a concurrent increase in incidence of testicular cancer, hypospadias, and cryptorchidism, has raised the question of possible environmental endocrine disruptors with oestrogenic or antiandrogenic actions influencing prenatal or neonatal testicular and genital tract development. The concern prompted the recent development of sensitive techniques for monitoring potential dele- terious reproductive effects of environmental chemicals. However, there is currently no evidence that the incidence of male infertility is increasing. Aetiologies Male infertility, comprising a heterogenous group of disorders, rep- resents the male partner’s contribution to the couple’s failure to con- ceive. This implied failure to fertilize normal ova is usually associated with defective spermatogenesis giving rise to absent (azoospermia) or low sperm output (oligospermia <20 million per ml) and/or ab- normal spermiogenesis giving rise to spermatozoa with poor motility (asthenozoospermia: <50% of spermatozoa showing progressive mo- tility) and abnormal morphology (teratozoospermia: <4% normal forms). The pathogenic basis of defective spermatogenesis or spermiogenesis remains poorly understood. Testicular histology may show quanti- tative reduction in all germ-cell types (hypospermatogenesis), Sertoli cell only syndrome, or maturation arrest at the primary spermatocyte (premeiotic) or spermatid (postmeiotic) stage. Idiopathic azoospermia/oligospermia By far the commonest form of male infertility (60%) is idiopathic azoo/oligospermia (absence of or too few sperm), usually asso- ciated with asthenozoospermia (reduced sperm motility) and teratozoospermia (sperm with abnormal morphology). This prob- ably represents the end result of a multitude of ill-defined patholo- gies which disrupt normal seminiferous tubular functions. However, recent molecular analyses have revealed that in many cases hitherto classified as idiopathic, there are discrete gene defects associated with impaired spermatogenesis. Asthenozoospermia Reduced velocity or vigour of sperm motility may be due to meta- bolic/functional defects or ultrastructural abnormalities in the axonemal complex of the sperm tail, usually associated with oligozoospermia or a high percentage of dead and abnormally- shaped sperm. The latter finding may indicate a recently recognized condition, epididymal necro/asthenozoospermia. Testicular sperm- atozoa are normal, the defects occurring during epididymal transit. Rarely, complete asthenozoospermia (with normal sperm density), may result from absence of dynein arms (sites of Na/K ATPase ac- tivity) linking individual microtubules. This is associated with similar defects in respiratory cilia and a history of chronic respiratory infection, bronchiectasis, and sinusitis (immotile cilia syndrome). In addition, some of these patients have situs inversus (Kartagener’s syndrome). Absence of the central pair of microtubules in the sperm

tail is an even rarer cause of complete asthenozoospermia—the 9+0 syndrome. Teratozoospermia An extreme example of abnormal sperm morphology is the failure of acrosomal cap development the sperm head, leading to forma- tion of rounded spermatozoa (globozoospermia) which are unable to bind to the zona pellucida, a prerequisite for fertilization. Chromosome disorders Chromosome abnormalities identified by cytogenetic studies of blood lymphocytes are found 15% of azoospermic patients, 90% of whom are found to have Klinefelter's syndrome. Other chromosomal abnormalities encountered include reciprocal X or Y autosomal translocations, XXY, and XX males, reciprocal and robertsonian autosomal translocations, supernumerary autosomes, and inversion of autosomes. Klinefelter's patients (XXY) are azoospermic. Spontaneous preg- nancies have been reported in the partners of such patients, usually in the context of 46 XY /47XXY mosaicism. The mechanism whereby an extra X chromosome gives rise to spermatogenic failure is un- clear. Inactivation of the X chromosome in primary spermatocytes is necessary for spermatogenesis to proceed normally through mei- osis. Hyalinized seminiferous tubules devoid of germ cells are perva- sive in the atrophic testes. Occasionally isolated foci of tubules with preserved spermatogenesis can be identified in the testicular biopsy of 47 XXY patients. These can be used for micro testicular sperm ex- traction (TESE) procedures and subsequent intracytoplasmic sperm injection to enable fertility in Klinefelter's syndrome patients. Y-chromosome micro deletions A major breakthrough in the understanding of the molecular genetics of male infertility was the characterization of three non- overlapping regions (designated azoospermic factors AZFa, AZFb, and AZFc) on the long on the Y-chromosome (Yq11), which con- tain multiple genes involved in spermatogenesis. Micro deletions in these AZFa loci, identifiable only by polymerase chain reaction (PCR) amplification of DNA but not routine karyotyping, have been found in 3 to 37.5% of patients previously considered to have idio- pathic azoospermia and severe oligozoospermia, but not in fertile control populations. Larger deletions (involving more than one AZF locus) are associated with more severe testicular phenotypes, and the incidence of microdeletions is highest among azoospermic pa- tients with Sertoli cell only histology. AZFc is by far the most fre- quently encountered deletion. Y-chromosome micro deletions are emerging as the second most common specific aetiology of male in- fertility (after varicoceles). Several cloned genes have been mapped to each of the AZF inter- vals. At least one strong candidate gene is associated with each dele- tion cluster (DFFRY in AZFa, RBMY in AZFb, and DAZ in AZFc). These are multicopy gene families scattered in both arms of the Y- chromosome, with the latter two expressed only in the testes. The specific products of these candidate genes and their functional sig- nificance remain unclear. Male infertility associated with micro

 deletions of Y chromatin is probably attributable to reduced copy number of more than one of these gene families. Other as yet un- identified genes important in spermatogenesis within or outside the AZF loci of the Y-chromosome are highly likely. Some patients with microdeletions of the Y-chromosome have oligozoospermia and not azoospermia. Transmission of specific Y-chromosome micro dele- tions to male offspring by assisted conception techniques has been clearly documented. Defects in target tissue Mutations in the ligand binding or DNA-binding domains of the androgen receptor cause defects in androgen action and varying degrees of failure of masculinization during primary sexual devel- opment (androgen insensitivity syndromes), despite raised levels of testosterone being produced by inguinal or intra-abdominal testes. These defects are, in descending order of severity: 1. Complete testicular feminization (female phenotype and female external genitalia with absent uterus and Fallopian tubes pre- senting with primary amenorrhoea) 2. Incomplete testicular feminization (female phenotype and fe-

male external genitalia with minimal virilization such as clitoral hypertrophy and partial fusion) 3. Reifenstein's syndrome (ambiguous genitalia with perineoscrotal hypospadias, poor penile development, bifid scrotum, and gy- naecomastia at puberty.). In contrast to the aforementioned points, extension of CAG polyglutamate repeats to greater than 40 in the N terminal domain of the receptor causes X-linked bulbar muscular atrophy (Kennedy's disease) associated with gynaecomastia, poor virilization, and azoo- spermia due to 'late-onset' androgen resistance. Expansion of CAG glutamine repeats to between 25 to 40 is associated with a fourfold increased risk of oligospermia or azoospermia without clinical evi- dence of neuromuscular degeneration. This may represent an exclu- sively testicular form of androgen insensitivity. Deficient 5 α-reductase type II action in the genital tract causes external genitalia that are often predominantly female at birth in combination with a male internal urogenital tract. There is typic- ally clitoral hypertrophy with perineoscrotal hypospadias, inguinal testes and epididymes, with ejaculatory ducts emptying into a blind ending vagina. Usually raised girls, these patients dramatically virilize at puberty without gynaecomastia. Males with oestrogen resistance and aromatase deficiency are normally virilized at birth and have normal pubertal development except for nonfusion of epiphyses resulting in extreme tall stature, and osteoporosis in adulthood. The effects on spermatogenesis and fertility are currently unclear. Cryptorchidism Cryptorchidism has a prevalence of 2.5–5% at birth, declining to 1% by one year. Spontaneous descent rarely occurs after this age. Undescended testes can be a feature of many hypogonadotropic conditions, intersexual and dysgenetic states such as androgen in- sensitivity syndromes, and Noonan's syndrome. The persistent Müllerian duct syndrome is caused by defects in anti-Müllerian hormone production or action during fetal development. The pres- ence of Fallopian tubes and uterus obstructs testicular descent. The lower temperature in the scrotum is a prerequisite for normal spermatogenesis. Undescended testes are therefore exposed to the harmful effects of the higher temperature in the abdomen and in- guinal region. A testis which is not permanently in a low scrotal pos- ition by the age of two years will sustain permanent damage to the seminiferous epithelium, hence orchidopexy after two years of age for undescended testes does not improve fertility. For these reasons, treatment should ideally be undertaken between one and two years of age. HCG or intranasal GnRH are being increasingly used for early initial treatment of cryptorchidism, with orchidopexy carried out by the age of two if this is unsuccessful. The risk of testicular tumour in a patient with a history of undescended testes, whether successfully treated by orchidopexy or not, is 4- to 5-fold higher than in the general population. Testicular tumours It is important to remember that infertility can be a presenting symptom of testicular tumours, the commonest malignancy in young adult men. With increasing use of a testicular ultrasound it has become clear that there is a significantly higher risk of testicular tumours in infertile men (in absence of cryptorchidism) compared to the general population. Carcinoma in situ, an obligatory precan- cerous state, is occasionally encountered incidentally in diagnostic testicular biopsies. Without treatment, 50% of carcinoma in situ progress to malignant seminoma or nonseminomatous germ-cell tumours. Varicocele Varicocele is a dilatation of the scrotal portion of the pampiniform plexus due to reflux of blood in the internal spermatic veins, usually involving the left side from the renal vein. It usually gives rise to a reduction in ipsilateral testicular volume, but varying degrees of hypospermatogenesis are often seen in both testes. Although a vari- cocele is clinically detectable in up to 40% of male partners of infer- tile couples, its significance in male infertility remains controversial. Increased scrotal temperature, hypoxia, and exposure of the testes to adrenal metabolites have been postulated as possible mechanisms by which spermatic vein reflux can induce seminiferous tubular damage. Since varicoceles can be detected clinically in 15% of fertile young men, it should not be assumed

that this condition is invari- ably or solely responsible for infertility without actively excluding other possible aetiologies, including those in the female partner. Sperm autoimmunity Immunological infertility is a specific disorder caused by sperm membrane-bound IgA antibodies found around 5% of men pre- senting with infertility. Conditions predisposing to sperm auto- immunity include vasectomy, testicular injury/inflammation, genital tract infections/obstruction, and family history of auto- immune disease. Male patients with significant antisperm anti- body titres usually have severely suppressed fertility potential due to sperm agglutination, poor sperm transit through cervical mucus, and blocked sperm-oocyte fusion. Genital tract infection Infection in the lower genital tract is a major cause of male infer- tility in a global context. Chlamydia, gonococcus, Gram-negative enterococci, and tuberculosis are the usual pathogens. If not treated by appropriate antibiotics promptly, inflammation of the accessory

13.6.2 Disorders of male reproduction and male hypogonadism 2403 gland's excurrent ducts may give rise to disturbed function, forma- tion of anti-sperm antibodies, and permanent structural damage with obstruction of the outflow tract. Asymptomatic prostatitis due to occult and usually focal infection is best diagnosed by transrectal ultrasound examination and culture of an ejaculate. Excurrent duct obstruction Vasectomy and previous genitourinary infections, usually sexually transmitted or tuberculous, are the most common causes of ob- structed azoospermia. Congenital bilateral agenesis of the Wolffian duct-derived structures—the corpus/cauda epididymis, vas def-erens and seminal vesicles (CBAVD)—is characterized by impalp- able scrotal vasa, distended caput epididymis, acidly noncoagulating semen of reduced volume (<2 ml) devoid of fructose and sperm, is present in 95% of males with cystic fibrosis. More commonly (6% of azoospermic men and 1–2% of infertile males), patients present with CBAVD without frank respiratory tract disease or pancreatic insufficiency. These have milder heterozygous mutations of the cystic fibrosis transmembrane regulator (CFTR) gene and /or the 5T variant in intron 8, giving rise to a predominantly genital phenotype of cystic fibrosis. Renal and urinary tract abnormalities are common in these patients. In Young's syndrome progressive epididymal obstruction is due to progressive inspissation of amorphous secretion in the lumen. In these patients, the high incidence of chronic sinopulmonary infection from childhood and bronchiectasis is presumably the consequence of the same abnormality in the respiratory tract. Epidemiological data has raised the possibility of mercury poi- soning as the cause of this condition. Coital disorders Inadequate coital frequency, technique (including the use of vaginal lubricants with spermicidal properties) and faulty timing of inter- course may contribute to continue infertility but are rarely the only etiological factor in the infertile couple. Diagnosis History Particular attention should be paid to the following aspects. Previous surgery such as herniorrhaphy in childhood, trauma, or torsion, suggest possible damage to the vas or testis. History of cryptorchidism and genitourinary infections are important etio- logical factors. Delayed onset of puberty may suggest the possi- bility of gonadotrophin deficiency. A history of recurrent chest infections, sinusitis, or bronchiectasis may be obtained in patients with epididymal obstruction (Young's syndrome), immotile cilia syndrome, and CBAVD associated with cystic fibrosis. Chronic disorders such as renal failure, liver disease, malignancy, diabetes mellitus, and multiple sclerosis are associated with a variety of tes- ticular and sexual dysfunctions. Patients should be asked about episodes of pyrexia within the past 12 weeks because of transient suppression of spermatogen- esis. Careful enquiry should also be made about occupational or environmental exposure to testicular toxins, current medications, previous and/or current use of recreational drugs. Painful ejacu- lation, haematospermia, and pain in the perineum are symptoms suggestive of chronic infection in the prostate and seminal vesicles. It is important

to establish that vaginal intercourse takes place with appropriate frequency, timing and without the use of the vaginal lubricants. Examination Assessment of height, weight, body habitus, and secondary sexual de- velopment should be carried out in all patients. Measurement of tes- ticular volumes by use of a Prader orchidometer provide a convenient clinical index of seminiferous tubular mass. Normal adult testicular volume ranges between 15 and 25 ml, and testicular volume is a key finding in differentiating between azoospermia due to seminiferous tubular failure (reduced volume) and that arising from excurrent duct obstruction (normal volume). Testicular size is also a useful indicator of the degree of testicular development in hypogonadotropic patients. If not in the scrotum, the lowest position of the testes should be de- fined with the patient upright. Irregular contour, induration, or ab- normal consistency of the testis suggest previous orchitis, surgery, or malignancy. Special attention should also be paid to the palpation of the epididymis and scrotal vas. An enlarged caput epididymis may be palpable in cases of obstructive azoospermia. Irregularity and indur- ation of the epididymis and vas suggest previous infection. In con- genital agenesis of the Wolffian duct-derived structures, the scrotal vasa are either impalpable or extremely thin. The patient should be examined standing so that varicoceles can become visible (grade 3) or palpable (grade 2), or detected as a venous impulse in the spermatic cord during Valsalva manoeuvre (Grade 1). Rectal examination may detect irregular contour or abnormal consistency and tenderness in the prostate in the presence of chronic prostatitis, and enlarged sem- inal vesicles due to ejaculatory duct obstruction. Investigations Conventional parameters of the semen analysis such as sperm density, percentage of motile sperm, quality of sperm movements, and sperm morphology provide a semiquantitative index of fertility potential. Although a variety of tests of sperm function, such as com- puter aided sperm movement analysis, cervical mucus penetration, acrosome reaction, sperm-zona pellucida binding, and hamster oo- cyte penetration, have been devised, none is sufficiently reliable and accurate to be used routinely in clinical practice. Infertile men with oligozoospermia produce spermatozoa harbouring abnormal DNA with strand breaks and redundant cytoplasm, which may produce excess reactive oxygen species. Chromatin structure and cytoplasmic enzyme (LDH-X or CK-M) assays are being applied to assess functional integrity of sperm- atozoa, and these may provide more reliable quantitative biochem- ical measures of male fertility to guide management in the future. Measurement of plasma FSH is useful in distinguishing pri- mary and secondary testicular failure and in identifying patients with obstructive azoospermia. In the presence of azoospermia or oligozoospermia, an elevated FSH, particularly with reduced tes- ticular volume, is presumptive evidence of severe and usually ir- reversible seminiferous tubular damage. Low or undetectable FSH (usually associated with low LH and testosterone with clinical evi- dence of androgen deficiency) is suggestive of hypogonadotropic hypogonadism. Conversely, azoospermia with normal FSH and a normal testicular volume usually indicates the presence of bilateral genital tract obstruction. The potential role of inhibin B measurement as a circulating marker of Sertoli cell function in routine diagnostic workup of male

 infertility is currently being evaluated. Testosterone and LH meas- urements are only indicated in the assessment of the infertile male when there is clinical suspicion of androgen deficiency, Klinefelter’s syndrome, or sex steroid abuse. A high LH and testosterone should raise the possibility of abnormalities in androgen receptors, while low LH and testosterone suggest gonadotrophin deficiency. Hyperprolactinaemia is not a recognized cause of male infertility but prolactin measurement should be undertaken if there is evidence of sexual dysfunction (particularly diminished libido) or pituitary dis- ease leading to secondary testicular

failure. Oestradiol measurement is rarely indicated, except in the presence of gynaecomastia. Chromosomal analysis by karyotyping or fluorescent in situ hy- bridization should be carried out in patients with azoospermia, tes- ticular atrophy and elevated FSH, primarily to confirm the diagnosis of Klinefelter's syndrome. Screening for Y-chromosome micro dele- tions should be considered in all patients with sperm density of less than 5 million/ml by an appropriate number of PCR based DNA markers and confirmed by Southern blotting. The need for testicular biopsy has largely been superseded by the use of plasma FSH in recent years to differentiate between primary testicular failure and obstructive lesions. Undetectable or very low levels of seminal fructose is used to con- firm the clinical diagnosis of congenital bilateral absence of the vas deferens (CBAVD) or blocked ejaculatory ducts in the presence of obstructive azoospermia. An increasing number (more than 1 mil- lion/ml) of peroxidase-positive or monoclonal antibody-detected leucocytes in the semen may indicate genital tract infection. Semen culture for pathogens is difficult because of the bactericidal prop- erties of seminal plasma and the presence of urethral and skin commensals. Antisperm antibodies are detected by mixed agglutination reac- tion where either sheep red blood cells or polyacrylamide beads are coated with rabbit antibodies to specific classes of human Igs. These will attach to motile spermatozoa carrying specific IgA on the sur- face of the sperm head or tail. Ultrasound examination of the testes has become a routine inves- tigation for infertile males with nonobstructive azoospermia or se- vere oligospermia, or to detect occult testicular tumours. In patients with persistent or treated cryptorchidism, testicular ultrasound should be carried out annually. Ultrasound of the urinary tract is indicated in patience with CBAVD. Transrectal ultrasound can aid the diagnosis of asymptomatic chronic prostatitis. Management Pregnancies can occur in subfertile couples without treatment, al- beit with a much-reduced probability depending on the duration of infertility, age and coexisting subtle abnormalities in the female partner, in addition to any defects in sperm quality. Since most pa- tients with male infertility present no recognizable or reversible aeti- ologies, management remains largely empirical. Subfertility due to idiopathic hypospermatogenesis Although a wide variety of empirical medical treatments, including gonadotrophins, androgens, and antioestrogens have been tried in attempts to improve fertility in subfertile men, none has been shown to be effective when assessed in randomized control thera- peutic trials and are therefore none are recommended. Instead, as- sisted conception techniques are increasingly applied to overcome idiopathic male infertility. This is based on the premise that placing a large number of prepared motile spermatozoa in close proximity to ovulated or retrieved oocytes in vivo or in vitro can enhance the probability of fertilization. Intrauterine insemination (IUI) of more than 1 million washed and motile spermatozoa (freed of seminal plasma, leucocytes, and abnormal/dead spermatozoa) is a rela- tively simple and inexpensive techniques with few complications. Pregnancy rates of 5–10% per cycle can be expected. This can be combined with controlled ovarian stimulation of the female using gonadotrophin, but the risk of multiple pregnancies increases. In vitro fertilization (IVF) involves more intensive gonadotrophin simulation of the female, suppression of spontaneous ovulation using a GnRH antagonist, and collection of multiple oocytes by laparoscopy or transvaginal ultrasound guided ovarian puncture, which are then coincubated with prepared spermatozoa in culture medium. In patients with moderate oligozoospermia, average fer- tilization rates of 30% and live birth rates of 5 to 12% per treatment cycle can be anticipated. In those with severe and multiple defects in semen parameters, standard IVF is less effective. For these cases, microinjection of single live spermatozoa directly into harvested oocytes (intracytoplasmic sperm injection, ICSI) has become the treatment of choice. This by- passes the sperm-oocyte interactions normally required for fertil- ization in natural conception or IVF and can achieve a remarkably high fertilization and live birth

rates (55 and 26% per cycle respect- ively), even with the most severely abnormal samples. Since only a few spermatozoa are required, ICSI has revolutionized management of extreme oligozoospermia and azoospermia irrespective of aeti- ology. Nonobstructive azoospermia is frequently intermittent and careful examination of centrifuged deposits of semen to detect and harvest occasionally ejaculated spermatozoa for ICSI should be at- tempted repeatedly before resorting to alternatives. Even in patients with persistent nonobstructive azoospermia, isolated foci of sperm- atogenesis may be preserved so that testicular sperm extraction by multiple biopsies can often yield viable testicular spermatozoa (including several patients Klinefelter syndrome) for ICSI, and in persistent obstructive azoospermia epididymal spermatozoa can be aspirated by an open procedure or percutaneous needle punching of the proximal epididymitis. In these circumstances, cryostorage of harvested spermatozoa for subsequent ICSI is required. This does not appear to compromise efficacy. In children born after successful ICSI treatment, the incidence of major congenital abnormalities are not increased compared with natural pregnancies, but there is a small increase in sex chromosome aneuploidy in some series. Concern re- garding the developmental potential of children born after ICSI has been raised and long-term follow-up of ICSI births is indicated. Specific treatable conditions Removal or withdrawal from antispermatogenic agents or drug ex- posure may lead to improvement in fertility. This is most frequently seen in patients with inflammatory bowel diseases, when changing treatment from sulphasalazine to 5-aminosalicylic acid removes the offending moiety, sulphapyridine. Withdrawal from anabolic ster- oids abuse invariably leads to recovery of spermatogenesis, although this may take several months because of the long half-lives of some agents. Cryopreservation of semen should be offered to all male pa- tients of reproductive age before commencing anticancer chemo- therapy or testicular irradiation.

13.6.2 Disorders of male reproduction and male hypogonadism 2405 When patients with hypogonadotropic hypogonadism desire fer- tility, they can discontinue exogenous androgen replacement and start on human chorionic gonadotropin (HCG 1500–2000 IU sub- cutaneously twice weekly) for 6 to 12 months. This should maintain normal testosterone concentrations. Patients with postpubertally acquired gonadotrophin deficiency (e.g. from pituitary tumour), where spermatogenesis has been previously established, usually re- spond to HCG treatment alone to reinitiate germ-cell development. If there are no spermatozoa in the ejaculate at the end of 12 months, human menopausal gonadotrophin (HMG), which contain both FSH/LH or recombinant FSH (Puregon, Gonal F), should be added at 75 to 150 international units SC thrice weekly. Combined treat- ment may be required for a further 12 months. Most patients with congenital forms of hypogonadotropic hypogonadism will require FSH to stimulate Sertoli cell division and initiate spermatogenesis. In general, around 70% should show active spermatogenesis and 50% could be expected to achieve spontaneous pregnancies in their partners, even if sperm density remains in the oligospermic range. Patients with hypothalamic GnRH deficiency can be treated by pul- satile GnRH delivered two-hourly by a battery driven portable in- fusion minipump, although many find this form of chronic therapy impractical and too demanding. The outcome of treatment is similar to that obtained with exogenous gonadotrophin therapy. Active infection in the genital tract should be treated with ap- propriate antibiotics (erythromycin, doxycycline, norfloxacin) for four weeks for the patient and his partner. Obstructive azoo- spermia due to epididymal obstruction can be treated by micro- surgical epididymovasostomy, but high pregnancy rates are only be achieved by experienced microsurgeons. A more feasible alterna- tive is to obtain spermatozoa from the caput epididymis or efferent ducts proximal to the site of obstruction by direct needle aspiration (microepididymal sperm aspiration or percutaneous epididymal sperm aspiration) for use in assisted fertilization procedures (usu- ally ICSI). In patients with CBAVD, CFTR mutation

screening of the partner and genetic counselling should be undertaken beforehand because of the risks of cystic fibrosis in offspring. Sperm antibody can be treated by suppression with high-dose prednisolone (0.75 mg per kilogram per day, or prednisone 20 mg twice daily on days 1 to 10 and 5 mg on days 11 and 12 of the partner's cycle for 3 to 6 cycles). Side effects are common, including irritability, sleeplessness, arthralgia, muscle weakness, peptic ulceration, glucose intolerance, and aseptic necrosis of fem- oral head. Result of controlled trials have been conflicting. IVF and ICSI are increasingly being applied to manage immunological male infertility. Varicocele can be treated either by open surgical ligation or transfemoral embolization of the internal spermatic veins. Results of treatment of varicocele in eight prospective controlled therapeutic trials are confusing. Coexisting female factors contributing to infer- tility, insufficient sample size, high dropout rates, and lack of ran- domization/blinding or sham procedures, are some of the more important confounding variables which typify difficulties of treat- ment trials in male infertility. Nevertheless, the Royal College of Obstetricians and Gynaecologists concluded that treatment of vari- cocele in oligozoospermic but not normospermic subfertile men can significantly improve semen quality and pregnancy rates. The cost of varicocele treatment per live birth is less with surgical ligation (and embolization) than for assisted conception techniques. Retrograde ejaculation can be treated medically with oral sym- pathomimetics and anticholinergics, but evidence of their efficacy is limited. If unsuccessful, spermatozoa can be recovered by bladder catheterization and after irrigation with culture medium used for artificial insemination or IVF. Semen can be obtained by mastur- bation, vibrators, or electroejaculation from patients with various coital dysfunctions. Untreatable sterility Patients with persistent nonobstructing azoospermia without re- trievable postmeiotic germ cells, unable to undergo or failed to be helped by ICSI, should be counselled regarding the options of con- tinuing childlessness, adoption, and donor insemination. Genetic screening and counselling This has become important with the realization that genetic dis- orders account for an increasing proportion of infertility previ- ously believed to be idiopathic, and that there is a high probability of transmitting infertility to male offspring if assisted reproductive treatment is successful. Furthermore, the long-term health of ICSI offspring remains an unsettled question. All couples considering micro assisted fertilization techniques should therefore be coun- selled. It is also recommended that chromosomal karyotyping and Y-chromosome screening be performed in patients with azoo- spermia and severe oligozoospermia (<5 million per ml), regardless on the coexistence of other clinical abnormalities such as varicocele or cryptorchidism. This not only allows a firm diagnosis to be made, but also encourages the clinician to forego empirical treatment and couples who have conceived by assisted reproduction techniques can inform their son at suitable age that he is likely to have fertility problems. As stated previously, patients with obstructive azoo- spermia due to CBAVD and their partners should undergo CFTR gene screening followed by a genetic counselling if positive. Erectile dysfunction Erectile failure maybe caused by neurological disorders such as autonomic neuropathy (usually complicating diabetes mellitus), multiple sclerosis, and spinal injuries, as well as vascular disease involving pelvic vessels, retroperitoneal and bladder neck surgery, medications (commonly α- and β- adrenergic antagonists, psycho- tropic agents), alcohol abuse, severe systemic disease, psychological dysfunction (including depression), relationship problems, an- drogen deficiency, and hyperprolactinaemia. Loss of libido charac- terizes androgen deficiency and hyperprolactinaemia, while normal spontaneous morning erection is suggestive of psychogenic impo- tence. Testosterone deficiency is uncommon (less than 5%) in pa- tients who presents with erectile dysfunction without loss of libido. Management should aim to correct reversal of any underlying cause (e.g. prolactinoma treated by a dopamine agonist) or substi- tute offending medications. Androgen replacement is only indicated in patients with total or free plasma testosterone in the

hypogonadal range. The use of a phosphodiesterase inhibitor (PGE5 inhibitors) such as sildenafil, tadalafil, vardenafil, and avanafil to enhance the neurovascular cGMP-mediated nitric oxide smooth muscle relax- ation in penile vasculature is a remarkably successful way of treating a wide variety of erectile dysfunction. In refractory cases vacuum devices and intracavernous injection of vasodilator agents such as PGE1 can be considered.

Revision #1
Created 2026-01-22 16:37:55 UTC by Omar Ayman
Updated 2026-01-22 16:37:55 UTC by Omar Ayman