13.6.1 Ovarian disorders 2374 Stephen Franks, Kate

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male hypogonadism 2386 P.-M.G. Bouloux 13.6.3 Benign breast disease 2406 Gael M. MacLean 13.6.4 Sexual dysfunction 2408 Ian Eardley 13.6.1 Ovarian disorders Stephen Franks, Kate Hardy, and Lisa J. Webber ESSENTIALS The ovary produces (1) oocytes—germ cells in the ovary have under- gone the first meiotic division to become oocytes in primordial fol- licles by the time of birth, with about 400 of these ovulating during reproductive life; and (2) hormones—oestradiol, progesterone, an- drogens, and two nonsteroidal glycopeptides, inhibin A and B. Ovulation and hormonal secretion are regulated by the pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), production of which is controlled by pulsatile release of the decapeptide gonadotropin-releasing hormone from the hypo- thalamus. LH and FSH act on maturing ovarian follicles: LH inducing androgen secretion from the thecal layer, and FSH stimulating the inner granulosa cell layer to aromatize androgens to generate oestro- gens. After ovulation, the corpus luteum produces oestradiol as well as progesterone: these two hormones, together with inhibins, exert feedback inhibition on gonadotropin release. In the normal menstrual cycle, differential sensitivity to FSH leads to enhanced growth of a dominant follicle which becomes respon- sive to LH, with enhanced steroidogenesis and greatly increased oes- tradiol concentrations. This triggers a surge in LH, a positive feedback phenomenon that induces resumption of meiosis in the oocyte and ovulation by rupture of the follicle, which is then induced to secrete abundant progesterone. Progesterone suppresses gonadotrophin release and—if trophoblastic gonadotrophin secretion fails to occur (in the absence of fertilization and pregnancy)—the corpus luteum breaks down, inducing the onset of a new cycle. Involuntary infertility affects about 15% of couples, with ovulatory disorders accounting for 25 to 30%. Disorders of ovulation Disorders of ovulation usually result in perturbation of normal cyc- lical

menses, leading to amenorrhoea, oligomenorrhoea (more than 6 weeks between periods) or very irregular menses. Aetiology—the condition may be (1) primary—menarche de- layed beyond 16 years, no previous periods; may be caused by developmental disorders; or (2) secondary—at least one previous spontaneous period; causes include premature (primary) ovarian in- sufficiency, hypothalamic/pituitary dysfunction, and polycystic ovary syndrome, which is the commonest cause of oligomenorrhoea. Premature (primary) ovarian insufficiency —defined as ovarian failure at less than 40 years; cause unknown in most cases but may be associated with organ-specific autoimmune diseases, chromosomal abnormalities (e.g. Turner syndrome, 45X) or be iatrogenic (young adult cancer survivors); high FSH, low oestrogen; often treated with hormone replacement therapy, but oocyte donation is the only op- tion for conception. Hypothalamic/pituitary disorder—characterized by low FSH, low oestrogen; most commonly related to (a) weight loss—often as- sociated with an underlying eating disorder; fertility treatment is unwise until normal body mass index has been achieved; or (b) hyperprolactinaemia. Polycystic ovary syndrome—typically presents with amenorrhoea in association with clinical signs of hyperandrogenism (hirsutism, persistent acne, male-pattern alopecia); wider definition requires two of (1) oligo- and/or anovulation, (2) clinical and/or biochem- ical signs of hyperandrogenism, and (3) polycystic ovaries. Is as- sociated with a metabolic disorder including insulin resistance/ hyperinsulinaemia/impaired glucose tolerance and dyslipidaemia. Management is mainly targeted at relief of symptoms/complications with diet, antiandrogens (e.g. cyproterone acetate, spironolactone). Anovulatory women who wish to conceive usually respond to ovula- tion induction therapy (e.g. clomiphene). 13.6 Reproductive disorders

13.6.1 Ovarian disorders 2375 Hirsutism Mild to moderate long-standing hirsutism in women with regular menses is very likely to be associated with polycystic ovary syn- drome, which can be confirmed by finding normal/slightly elevated serum testosterone concentration and pelvic ultrasonog- raphy to determine ovarian morphology. Patients with a short history of hirsutism (particularly if severe), symptoms suggesting other endocrine disorders (e.g. Cushing’s syndrome), and/or serum testosterone above 5 nmol/litre
(normal range 0.5–3.0) require further investigation including ovarian and/or adrenal imaging (for androgen-secreting tumour) and biochemical tests for Cushing’s syndrome and congenital ad- renal hyperplasia. Introduction Ovarian disorders are very common. Involuntary infertility affects an estimated 15% of couples and disorders of ovulation account for 25–30% of the causes of infertility. In most cases, disorders of ovulation are attributable to a treatable, endocrine abnor- mality. Indeed, polycystic ovary syndrome, a major contributor to endocrine-related infertility, is the commonest endocrine disorder in women, with a prevalence in excess of 5% in the female popu- lation of reproductive age. Disorders of ovarian function usually manifest themselves as irregular, infrequent, or absent menses. Hirsutism, or excess, male-pattern body hair is another common manifestation of ovarian (and, less often adrenal) dysfunction. In the following chapter, ovarian development, the physiology of the hypothalamic–pituitary–gonadal axis, and the hormonal changes of the normal menstrual cycle will be described as a preface to the description of disorders of ovulation, their investigation, and man- agement. The causes, investigation, and management of hirsutism will also be elucidated. Ovarian development Ovarian development is essentially complete by about six months of fetal life and at this time the ovaries contains some 6–7 million germ cells. By the time of birth, the number of germ cells has fallen to 1–2 million and the remaining germ cells have entered the first meiotic division to form oocytes. Each oocyte is surrounded by a single layer of flattened, somatic (pregranulosa) cells, to form the primordial

follicle. It is the primordial follicles that constitute the ‘resting’ pool that must provide sufficient oocytes to last a normal reproductive lifespan. Ovarian organogenesis and follicle formation The fetal ovary is formed from three embryonic cell lineages: the coelomic epithelium, the mesenchyme of the mesonephros (primi- tive kidney) and primordial germ cells, which are first observed within the extraembryonic tissue of the yolk sac. At about four weeks the coelomic epithelium thickens over the mesial aspect of the mesonephros forming the gonadal ridge. The underlying mes- enchymal cells of the mesonephros also proliferate and the gonadal ridge protrudes into the coelomic cavity as the gonadal anlagen or primordium. Concurrently, primordial germ cells begin to migrate from the yolk sac with an amoeboid-like action. Before leaving the yolk sac, as well as en route, they divide by mitosis and enter the primordium. Once populated by primordial germ cells, the primor- dium becomes the indifferent gonad. This initial development of the ovary is identical to that of the testis until morphological changes occur at around the sixth week of embryonic life that makes the male and female gonad distinguishable. Evidence from the mouse indi- cates that primordial germ cells differentiate once they have reached the female gonad, lose their migratory ability, and are then known as oogonia. The distinct morphology of the ovary is recognizable by the end of the sixth week, a few days after that of the testis. Oogonia dramat- ically increase in number by mitosis, germ cell number reaching a maximum of about seven million at mid-gestation. Although mi- tosis can continue until birth, by the third trimester germ cell loss, occurring by apoptosis or (programmed cell death) exceeds the rate of mitosis and germ cell number falls. Proliferation of the coelomic epithelium forms protrusions into the mesenchyme which gives rise to the sex cords, surrounding nests of primordial germ cells/oogonia. Once enclosed by these cords of somatic cells, the germ cells cease mitosis and enter mei- osis several weeks after sex-specific gonadal differentiation. This division is arrested, one to two weeks later, at the diplotene stage of the first meiotic division, resulting in the formation of oocytes. The oocyte remains arrested in the first meiotic division and meiosis is completed only in the mature follicle that is destined to ovulate. Resumption of meiosis is triggered by the surge of LH preceding ovulation, which may be many decades later. Newly formed oocytes become enclosed in a single flattened layer of somatic, pregranulosa cells surrounded by a basement membrane to form the primordial follicle (Fig. 13.6.1.1). Follicle formation begins close to the cortico-medullary boundary and primordial follicles appear to separate from the sex cords. Oogonia and oocytes that have not formed follicles by association 20 mm 0.2 mm Preantral (gonadotrophin independent) several months Antral (gonadotrophin dependent) 6 weeks Primordial Primary Secondary Early antral Graafian (preovulatory) Fig. 13.6.1.1 Follicle development in the human ovary. The various stages of preantral and antral (gonadotropin-dependent) development of the follicle are depicted ranging from the primordial (quiescent) stage in which the oocyte is enclosed in a single layer of pregranulosa cells, to the preovulatory stage. This process takes several months. Adapted from Hardy K, et al. (2000). In vitro maturation of oocytes. Br Med Bull, 56, 588–602. Copyright (2000), with permission from Oxford University Press.

section 13 Endocrine disorders 2376 with somatic cells generally remain within the sex cords, where they undergo apoptosis. The origin of granulosa cells is still not completely certain, and may vary from one species to another but it is likely that they are derived from the ovarian surface epithelium. Follicle development in the normal ovary Primordial follicles provide the ‘stock’ of oocytes which must last for up to 50 years. Initiation of follicle growth (i.e. progression of the follicle from the primordial to the early growing phases) must be tightly regulated to ensure a steady supply of oocytes for ovula- tion during a normal reproductive life-time. However, the

factors responsible for controlling initiation of growth are yet to be deter- mined. The first indication of growth of the follicle is proliferation and a resultant change in shape of the granulosa cells, which be- come more cuboidal in appearance (Fig. 13.6.1.1). Follicles pass through a transitional, or intermediary, stage in which a propor- tion of the granulosa cells are cuboidal, and the rest remain flat- tened. This is followed by the primary stage in which the oocyte is enclosed in a single layer of completely cuboidal cells. By this stage, the oocyte has increased significantly in volume. Follicle develop- ment progresses by formation of a second layer of granulosa cells, and at this stage the first theca cells, derived from surrounding stroma, begin to organize around the granulosa layer. This is fol- lowed by formation of further layers of granulosa and theca cells (with enlargement of the oocyte) to form a multilayered preantral follicle. The outer layers of the theca comprise cells which are similar to those in surrounding stroma and constitute the theca externa. The cells of the inner layers become polyhedral and form the theca interna, the site of androgen production in large preantral and antral follicles. Eventually, the theca interna of each follicle receives its own blood supply. Development of the follicle to the multilayered preantral stage can progress without the need for gonadotropins. It is unclear how long it takes for a follicle to pro- gress from the primordial to large preantral follicle, but estimates suggest that this may be at least three months. Granulosa cells continue to proliferate, and a fluid-filled space (the antrum) eventually forms between them and continues to en- large: it is now an antral follicle, and this is the stage at which the gonadotropins take over as the major regulators of follicle develop- ment (Fig. 13.6.1.1). It is from this stage that the greatest expansion of the follicle occurs, in terms of granulosa and theca cell numbers, antrum size as well as oocyte growth and overall follicle diameter. Follicles that reach this stage are considered to be part of a ‘select- able’ follicle pool from which the so-called ‘dominant’ follicle will arise (i.e. that which is the most likely to complete maturation and ovulate). This pool may number 10–15 follicles between the two ovaries in young women and declines with age, averaging 10 at 30 years and 5 at 40 years. It will be evident that only a small frac- tion of the total pool of follicles is destined to ovulate. The rest will undergo atresia (death by apoptosis) along the way. Although it is likely that follicle loss by atresia occurs at all stages of follicle devel- opment, the highest proportion of atretic follicles is seen during the gonadotropin-dependent, antral stages. As described later, selection of a single follicle for ovulation in the human menstrual cycle, inev- itably involves regression and demise of subsidiary follicles within the same cohort. The hypothalamic–pituitary–ovarian axis Like the testis, the ovary has two major functions: (1) the produc- tion of gametes and (2) the secretion of hormones (particularly sex steroids) that affect development and function of the reproductive tract, as well as having important peripheral effects on muscle, bone, and skin. Like all classic endocrine organs, the function of the ovary is dependent upon regulation by pituitary hormones, which, in turn are regulated by hypothalamic signals (Fig. 13.6.1.2). Gonadotropin-releasing hormone (GnRH) is a decapeptide, secreted by the hypothalamus in a pulsatile manner, the frequency of pulses (between 60 and 180 minutes, according to the stage of the menstrual cycle), having a profound influence on the response of the pituitary gonadotropins (which are glycoprotein hormones) to GnRH. The episodic secretion of GnRH is reflected in the pattern of circulating gonadotropins, the ‘pulses’ of luteinizing hormone (LH) being more discrete than those of follicle-stimulating hormone (FSH) because of the shorter half-life of LH in the circulation. LH and FSH act in con- cert on the maturing large ovarian follicles. LH stimulates the theca layer of the follicle to produce androgens (androstenedione and tes- tosterone) while FSH acts specifically on the inner, granulosa cell layer of the mature follicle—which lacks the capacity to synthesize androgens—to convert androgens to oestrogens (the so-called two- cell, two gonadotropins hypothesis). Following ovulation, oestradiol

continues to be produced by the corpus luteum but the principal circulating steroid at this stage of the cycle is, of course, proges- terone. Oestradiol, during the mid-follicular phase of the cycle (see Hypothalamus LH FSH Oestradiol Progesterone Ovary Blood Pituitary (GnRH) Gonadotrophin releasing hormone − + Fig. 13.6.1.2 The hypothalamic–pituitary–ovarian axis. Courtesy of Prof K Hardy.

13.6.1 Ovarian disorders 2377 next section) and progesterone (luteal phase) exert a negative feed- back effect on both pituitary and hypothalamus to inhibit the secre- tion of gonadotropins. The ovary also produces two closely related, nonsteroidal (glycopeptide) hormones that selectively inhibit FSH and contribute to negative-feedback inhibition: inhibin B (produced by developing follicles in the follicular phase) and inhibin A (pro- duced mainly by the corpus luteum). The extraordinary feature of the hypothalamic–pituitary–ovarian axis is the phenomenon of 'positive feedback' stimulation of gonadotropins by oestradiol in mid-cycle, which results in the LH 'surge' and ovulation, as described next. The menstrual cycle The endocrine events of the menstrual cycle are summarized in Fig. 13.6.1.3. At the beginning of each normal cycle (convention- ally taken as the first day of menses), there is a cohort of follicles, ranging between 2 and 5 mm in diameter, which are dependent on, and responsive to FSH. Between the late luteal phase of the previous cycle and the early follicular phase, the negative feedback signal pro- vided primarily by progesterone is removed and the concentrations of FSH rise. This intercycle rise of FSH exceeds a notional threshold level that encourages follicle maturation. Of the cohort of follicles that arrive at this FSH 'window', only one (or occasionally two) is destined to complete the journey to ovulation. This is the follicle that is most responsive to FSH. It is often the largest of the cohort but not necessarily so. As the follicles grow in response to FSH, oestradiol (and inhibin B) levels rise in the circulation and exert a negative feedback effect on FSH. As a result of the fall in FSH in the mid-follicular phase, most of the follicles in the cohort will re- gress and die by atresia, leaving only the most FSH sensitive, 'dom- inant' follicle to continue to grow and to secrete oestradiol. By this time, the granulosa cells of the dominant follicle have acquired LH receptors (the only time in the life of the follicle when this occurs) and are also responsive to LH. The dual effect of FSH and LH en- hances granulosa cell differentiation and steroidogenesis so that in the preovulatory phase of the cycle serum oestradiol levels in the cir- culation have increased more than 10-fold compared with the early follicular phase, 95% of circulating oestradiol being attributable to that single preovulatory follicle. The steeply rising levels of oestra- diol (probably assisted by a small increase in circulating proges- terone, indicating granulosa cell, and perhaps oocyte 'maturation') then trigger the LH surge—the only example of a positive feedback effect of a target hormone on the hypothalamic-pituitary unit. The LH surge has three main functions: (1) it triggers resumption of mei- osis in the oocyte ready for fertilization, (2) it leads to follicle rupture and ovulation and (3) it stimulates formation of the corpus luteum, converting the follicle from a mainly oestrogen-producing unit to a highly vascularized, progesterone-producing 'factory'. Progesterone suppresses gonadotropins during the luteal phase and finally, if con- ception does not occur, luteolysis ensues after an apparently prepro- grammed interval of 12–14 days, triggering the onset of a new cycle. 5 8 6 4 2 0 0 50 0 10 15 Follicle diameter (mm) 20 Menses Oestradiol 0 26 1 5 10 15 Days of cycle 20 25 28 100 200 300 400 Oestradiol (pg/ml) Progesterone (ng/ml) FSH LH (U/litre) LH FSH Progesterone Menses CL Ovulation 25 Fig. 13.6.1.3 The human menstrual cycle. Adapted from 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, with permission from John Wiley and Sons Inc.

section 13 Endocrine disorders 2378 Disorders of ovulation Clinical presentation and causes of anovulation Disorders of ovulation usually result in perturbation of normal cyclical menses. It is uncommon to have regular but anovula- tory cycles, the exception being during adolescence when cyclical ovarian activity without ovulation (a feature of ‘immaturity’ of the hypothalamic–pituitary–ovarian axis) is characteristic of the early months post menarche. Thus, anovulation is generally characterized by amenorrhoea, oligomenorrhoea (more than 6 weeks between periods) or very irregular menses. Amenorrhoea may be primary (i.e. no previous periods) or secondary (at least one previous spon- taneous period). Primary amenorrhoea is less common and al- though its causes overlap with those of secondary amenorrhoea, it is not surprising that disorders of development of the ovaries and/ or reproductive tract are overrepresented in this category. In some cases, primary amenorrhoea (defined as menarche delayed be- yond 16 years of age) is accompanied by delayed pubertal develop- ment. Menstrual disturbance may be accompanied by symptoms of oestrogen deficiency, including vaginal dryness and hot flushes. Interestingly, vasomotor symptoms are common in women with premature ovarian insufficiency (POI) but not in younger women with POI or those with oestrogen deficiency due to hypothalamic-pituitary dysfunction. Patients with hyperprolactinaemia may complain of inappropriate lactation (galactorrhoea) but it is im- portant to recognize that this affects only 30–50% of women with hypersecretion of prolactin. Menstrual abnormalities accompanied by symptoms of androgen excess—hirsutism, acne, or alopecia—are typical of polycystic ovary syndrome. The causes of amenorrhoea are summarized in Table 13.6.1.1. The most prevalent cause of secondary amenorrhoea is that caused by hypothalamic and/or pituitary dysfunction. Hyperprolactinaemia, weight loss-related, and idiopathic amenorrhoea are all associated with a functional, rather than structural, hypothalamic disorder of gonadotropin regulation (see later). Polycystic ovary syn- drome accounted for a further 32% of cases and primary ovarian failure for 11%. Among women presenting with oligomenorrhoea (Table 13.6.1.2), the underlying cause was polycystic ovary syn- drome in the great majority of cases, making this syndrome the most common overall cause of anovulation, as discussed in more detail next. Differential diagnosis of amenorrhoea and oligomenorrhoea Examination should include routine measurement of height and weight and calculation of body mass index. With the aid of a small number of endocrine investigations, it is usually possible to dif- ferentiate between the various causes of ovarian disorders and to guide management (Table 13.6.1.3). Measurement of serum FSH will distinguish premature ovarian insufficiency (wherein FSH is elevated) from other causes of amenorrhoea and oligomenorrhoea (in which FSH is normal or low). Assessment of oestrogen status is an important step in investigation of women with amenorrhoea. This can be achieved by direct measurement of serum oestradiol, by ultrasound measurement of endometrial thickness or by a proges- togen challenge test. Serum oestradiol measurements are valuable if results are unequivocally low (i.e. lower than in the early follicular phase) or normal (equivalent to mid-follicular phase levels) but concentrations in the early follicular phase range may not exclude chronic oestrogen deficiency. The advantage of ultrasound scan- ning or the progestogen challenge test is that these provide what amounts to an in vivo bioassay of endogenous oestrogen action (on the endometrium). A combination of low oestrogen and low (or normal) FSH is indi- cative of hypothalamic/pituitary dysfunction. In such cases, serum prolactin should be measured and if elevated, pituitary imaging per- formed (see later and in Chapter 13.2.1). Overview of management of disorders of ovulation The simple schema for differential diagnosis of ovarian disorders provides a basis for selection of appropriate treatment, as outlined in Table 13.6.1.3. Details of management of the individual disorders are given in the appropriate following sections. The first principle must al- ways be to treat any underlying cause, if

possible; for example, helping women with weight loss-related amenorrhoea to gain weight. For women with POI (high FSH, low oestrogen), gamete donation is the only option for fertility treatment but oestrogen replacement (with a progestogen for endometrial protection when the uterus is present) is required for treatment of symptoms of oestrogen deficiency (see later). In women with a hypothalamic or pituitary cause of anovulation (low or normal FSH with low oestrogen), ovulation can be induced by gonadotropins or GnRH (or, in the case of hyperprolactinaemia by dopamine agonists), but patients not requiring fertility treatment will, like those with POI, need sex hormone replacement. Ovulation can be induced in most women with polycystic ovary syndrome (PCOS; normal FSH, normal oestrogen) by antioestrogens, but some may Table 13.6.1.1 Causes of amenorrhoea Primary ovarian failure (11%) Hypothalamic/pituitary dysfunction (55%) Hyperprolactinaemia (11%) Weight loss-related (35%) Idiopathic (9%) Polycystic ovary syndrome (32%) Genital tract disorder (2%) Table 13.6.1.2 Causes of oligomenorrhoea Polycystic ovary syndrome (87%) Peri-menopausal (3%) Recovered weight loss (9%) Uncertain cause (1%) Table 13.6.1.3 Differential diagnosis and guide to management of women with amenorrhoea Results of investigations Diagnosis Management High FSH, low oestrogen Primary ovarian failure Hormone replacement therapy (HRT) Normal/low FSH, low oestrogen —if prolactin high Hypothalamic/pituitary disorder Hyperprolactinaemia GnRH or FSH (or HRT) Dopamine agonists Normal FSH, normal oestrogen (± high LH) Polycystic ovary syndrome Clomiphene, FSH Cyclical progestogens or oral contraceptive

13.6.1 Ovarian disorders 2379 require gonadotropin therapy. In those not wishing to conceive, man- agement of erratic periods and treatment of attendant symptoms of androgen excess are important considerations. Premature (primary) ovarian insufficiency (POI) Amenorrhoea due to loss of ovarian function under the age of 40 years affects approximately 1% of women and is known as POI. Other terms that have been used for this condition include premature (or primary) ovarian failure, premature menopause, hypergonadotropic amenor- rhoea, and gonadal dysgenesis. It results from an irreversible prema- ture depletion of ovarian follicles, although it is not unusual to have episodes of spontaneous ovarian function. In a very small proportion of women with POI (up to 5%) this may even result in pregnancy. This is in contrast to the normal menopause, or last ever menstrual period, usually occurring after the end of the fifth decade (average age 51 years). Menopause is a normal physiological event, occurring as a result of permanent ovarian failure once the number of ovarian fol- licles falls below a critical number, believed to be about 1000. No data exist on follicle number at the onset of POI and in some rare causes of POI, ovarian follicles remain within the ovary but are unresponsive to gonadotropin stimulation (e.g. FSH receptor mutations). Normal menopause and POI share the characteristic endocrine features of oestrogen deficiency associated with elevated serum con- centrations of FSH (and LH). It is important to investigate the cause of POI as it may have im- portant other clinical implications for the individual and sometimes her family. Idiopathic Most cases of POI are idiopathic, and it is not clear if the underlying cause is related to an initial reduced population of primordial fol- licles within the fetal ovary, an increased rate of atresia throughout reproductive life or a combination of both. Smokers may experience menopause at a younger age than nonsmokers, although there is no evidence for causation in POI. Case reports have described various infections preceding POI (e.g. HIV, cytomegalovirus, tuberculosis, shigella), but only mumps oophoritis is considered causative, ex- plaining only a low percentage of cases of POI. Chromosomal and genetic Around 10% of POI is due to an abnormal karyotype, Turner syn- drome (45X) and its mosaic forms being the commonest. Turner syndrome (TS) usually results in delayed puberty and primary amen- orrhoea, but Turner mosaics may

undergo normal puberty and can present with secondary amenorrhoea, sometimes even over the age of 35 years. An oocyte requires two normal X chromosomes to protect it from early atresia: this is thought to be the mechanism leading to the depleted number of ovarian follicles in TS and TS mosaic females. TS females have a structurally normal vulva, vagina, uterus, Fallopian tubes, and ovaries, although the latter may be small. In contrast, in XY- gonadal dysgenesis (Swyer's syndrome) the 46XY karyotype invariable results in delayed puberty and primary amenorrhoea. A deletion on the Y chromosome results in a nonfunctioning streak gonad, which is un- able to produce anti-Müllerian hormone (AMH: normally a product of Sertoli cells in the fetal testis) and therefore the Müllerian structures do not regress. The result is an anatomically normal vulva, vagina, uterus, and fallopian tubes. The gonads are thought to be at increased risk of malignant change and surgical removal is usually recommended. The gonads often lie high on the pelvic side-wall or may even be found above the pelvis and can be removed laparoscopically. Autosomal dominant, autosomal recessive, and X-linked patterns of inheritance have also been described in primary ovarian failure. It is now recognized that the mutation responsible for Fragile X syndrome, a cause of mental retardation, can also cause premature ovarian failure in carriers, and Fragile X (FRAXA) 'premutations' are probably the most common genetic cause of ovarian failure. Women with POI should be offered FRAXA testing after appro- priate counselling, although it is not currently thought necessary to test routinely for autosomal gene mutations unless clinical features should suggest a particular underlying condition. It is important to investigate potential chromosomal and gen- etic causes of POI, as these may be significant in counselling family members or any children of affected women. In addition, there may be important clinical implications for the woman with POI attached to the underlying diagnosis. TS females are prone to congenital heart disease, aortic dissection, and their pregnancies (both natural and egg donation) are high risk. A minority of TS women (around 10%) may have a small amount of Y chromosome material present, which may put them at increased risk of gonadal malignancy. Iatrogenic Iatrogenic POI is increasingly seen in young adult cancer sur- vivors, especially of childhood haematological malignancies. Other common groups are young women with breast cancer having ad- juvant chemotherapy and those with cervical cancer treated with chemo/radiotherapy. Stem cell transplants (which require chemo-therapy) are being increasingly used for benign conditions such as β thalassaemia and multiple sclerosis. The cause is loss of germ cells and follicles as a consequence of chemotherapy and/or irradiation. Not all chemotherapy regimens are equally toxic to the ovary and the effects are variable. Alkylating agents, especially cyclophospha- mide and procarbazine, are particularly associated with subsequent reduced ovarian reserve and POI, although platinum-based agents, anthracyclines, and taxoids are less so and the antimetabolites (e.g. methotrexate, 5-fluorouracil) probably have the lowest risk. Ovarian surgery and oophorectomy for benign and malignant disease is another important cause of iatrogenic POI and whenever possible, fertility-sparing surgery should be performed. It is possible that endometriosis destroys ovarian follicles but surgical treatment to ovarian endometriosis may also have an effect, especially if per- formed repeatedly. Autoimmune POI may be associated with a range of autoimmune conditions, including thyroid disease, but the most clinically important one is with autoimmune Addison's disease. However, a direct autoimmune cause for POI, where there is histological evidence of inflammatory infiltration of the ovarian cortex, has only ever been described when steroid cell autoantibodies are identifiable in the peripheral blood. Treatment Treatment of POI falls into five categories: • induction of puberty (using low-dose oestradiol) in girls with de- layed puberty; • control of symptoms of oestrogen deficiency;

section 13 Endocrine disorders 2380 • preservation (or improvement) of bone mineral density; • fertility; • psychological. Hypo-oestrogenic symptoms include hot flushes and night sweats, dyspareunia, urinary frequency, and loss of libido. Bone mineral density is likely to be low in untreated POI and can be preserved and increased with exogenous oestradiol. Oestrogen replacement should be in the form of a sequential or continuous combined regimen if the uterus is intact: progesterone being required to protect the endomet- rium from the effects of unopposed oestrogen. The psychological impact of diagnosis can be devastating, with a sense of loss, low self-esteem, socioeconomic disadvantage, and overall reduction in quality of life. Life expectancy appears to be re- duced in women with POI, mainly due to cardiovascular disease, and although the evidence is sparse, oestrogen replacement may at- tenuate the effect. Oestrogen replacement should ideally be in the form of oestra- diol, the active component of which is the same as the main ovarian oestrogen, 17-β oestradiol. Conjugated equine oestrogens are prob- ably best avoided for women with POI. Some young women find the combined oral contraceptive pill (COCP) more acceptable than standard oestrogen replacement, which is marketed for older, nor- mally menopausal women. Compliance can be an issue, especially in the under 25s, and the pill can be a useful alternative. However, most COCPs contains the synthetic oestrogen, ethinyloestradiol, which is more potent and may carry slightly higher risks. In addition, symp- toms of low oestrogen may occur during the pill-free week. It may also be less beneficial for bone health and should not be used for in- duction of puberty. There are some new COCPs containing oestra- diol, but it is not known how the risk of venous thromboembolism compares to those containing ethinyloestradiol. In addition, if taken for 21 out of every 28 days, the overall dose of oestrogen provided is lower than that required. Another advantage, though, of relying on the pill for oestrogen replacement is that it is contraceptive, whereas conventional hor- mone replacement therapy is not. Although pregnancy in POI is uncommon, it may occur. Unplanned pregnancy for any women can be traumatic, but when it occurs in the context of POI, the re- sults can be particularly upsetting. An important part of the man- agement of POI is therefore contraceptive advice, if pregnancy is undesirable. In contrast, a woman who would welcome a preg- nancy can be reassured that hormone replacement treatment will not decrease her chances of a pregnancy occurring and may pos- sibly be facilitating by maintaining uterine health (an oestrogen- dependent organ). Fertility Sadly, no fertility treatment will assist conception for women with POI and oocyte donation is the only option. Pelvic irradiation is associated with a poor outcome of pregnancy, both natural and oocyte donation, because of attendant uterine damage. The endo- metrium may be unable to support implantation and even if preg- nancy occurs, obstetric risks are increased, including miscarriage, premature delivery, and intrauterine growth restriction. The risks of pregnancy must also be considered seriously for women with Turner syndrome as maternal deaths from aortic arch dissection have occurred and there appears to be an increased incidence of placental abruption. It is vital that women with TS in whom preg- nancy may occur are suitably assessed and cared for by a specialist team with appropriate expertise. Hypothalamic/pituitary dysfunction Most cases of amenorrhoea due to hypothalamic/pituitary dysfunc- tion are of hypothalamic, rather than pituitary origin, and most are a function of an underlying disorder. Weight loss-related amen- orrhoea is very common. Nutritional status is an important de- terminant of reproductive function and being underweight (BMI <19 kg/m2) is very likely to result in abnormalities in the pulsatile secretion of GnRH leading, in turn, to reduced frequency and amp- litude of LH and FSH pulses, and oestrogen deficient amenorrhoea. Cyclical ovarian function can usually be restored by weight gain, but this is often difficult to effect. In some cases, even once weight has been restored, there may still be a time delay of months or even years before periods resume. Most women with weight loss-related

amenorrhoea have an underlying eating disorder and it is often ne- cessary to seek the help of specialist psychological or psychiatric services. Fertility treatment should generally be delayed in under- weight women until a normal body mass index (or close to normal) has been achieved and maintained. This is because a low maternal BMI is associated with intrauterine growth restriction. Correction of oestrogen deficiency is usually appropriate while treatment to aid weight gain is underway. Hyperprolactinaemia is another common cause of oestrogen- deficient amenorrhoea (discussed in greater detail in Chapter 13.2.1). Amenorrhoea is the typical presenting symptom of hyper prolactinaemia. It is important to exclude primary hypothyroidism or concurrent medication as possible causes before embarking upon pituitary radiology. In particular, dopamine antagonists (e.g. pheno- thiazines and metoclopramide) are well-recognized causes of ele- vated serum prolactin. Magnetic resonance imaging is the preferred method of detecting pituitary abnormalities. A microadenoma of the pituitary may be found in up to 50% of women with hyperprolactinaemic amenorrhoea. Larger tumours (≥10 mm) are much less common. Management of hyperprolactinaemic amenor- rhoea, even in women with an obvious prolactinoma, is primarily by the use of long-acting dopamine agonists such as bromocrip- tine or cabergoline. These drugs lower prolactin, restore ovulatory function and, typically, reduce the size of prolactin-secreting tu- mours. Pituitary surgery is rarely needed, even in women with large prolactinomas. In about 10% of cases, the underlying cause of hypothalamic amenorrhoea is uncertain. Recent studies of women with idiopathic (or ‘functional’) hypothalamic amenorrhoea have suggested that this category of patients represent what is essentially a stress-related hypothalamic disorder. Such patients respond very well to cogni- tive behavioural therapy (CBT), which results in resumption of ovulatory cycles without the need for endocrine treatment. If CBT is unsuccessful, ovulation can be induced, by pulsed gonadotropin- releasing hormone (GnRH) or gonadotropins, in women seeking fertility treatment (Fig. 13.6.1.4). However, at the time of writing, there are no GnRH delivery systems available commercially. Otherwise oestrogen/progestogen replacement is desirable to treat symptoms of oestrogen deficiency and/or to maintain bone density.

13.6.1 Ovarian disorders 2381 Finally, it is important to recognize that other hypothalamic-pituitary disorders, while themselves being rare causes of amenor- rhoea, may first present with menstrual dysfunction. Congenital deficiency of GnRH, best illustrated by Kallmann syndrome (in which gonadotropin deficiency is associated with anosmia), often presents as delayed puberty but may manifest as primary amenor- rhoea in girls who have completed pubertal development. In the last decade, there has been an exponential increase in our know- ledge of the network of neuropeptides and their receptors that im- pact on the hypothalamic control of gonadotropin secretion. These include the network of kisspeptin, neurokinin B, dynorphin and their receptors (so-called KnDY neurones). Important informa- tion has emerged regarding mutations and polymorphism in genes coding for these neuropeptides and receptors that are responsible for most causes of hypothalamic congenital gonadotropin defi- ciency. Amenorrhoea is a common presenting symptom in women with acromegaly or Cushing syndrome. Hypothalamic tumours or granulomas may cause deficiency of not only GnRH but also other hypothalamic hormones. It is not necessary routinely to screen for these rarer causes of amenorrhoea, but it is important to be alert to features in history and examination that may suggest a more un- usual diagnosis. Polycystic ovary syndrome Polycystic ovary syndrome (PCOS) is the commonest of all the ovarian disorders and the commonest endocrine disorder in women of reproductive age, with a prevalence of greater than 5% in the gen- eral population. The typical clinical presentation is the association of features of anovulation or oligo-ovulation (amenorrhoea or men- strual irregularity) with clinical and/or

biochemical evidence of an- drogen excess (hirsutism, persistent acne, or male-pattern alopecia) in women with polycystic ovaries (Fig. 13.6.1.5). However, the recog- nition that there may be a broader spectrum of clinical and biochem- ical presentation has led to a revision of the diagnostic criteria for PCOS (see next). The aetiology of PCOS remains uncertain. There is strong evidence for an ovarian origin of androgen excess although the hypersecretion of adrenal androgens can also be found, albeit in the minority of patients with PCOS. Genetic factors clearly play a part in the aetiology of the syndrome. There is clustering of cases of PCOS within families and a twin study showed that the concord- ance of features of PCOS is significantly greater in identical than in nonidentical twins. The mode of inheritance is unclear, but it is not a simple Mendelian trait. Rather, like type 2 diabetes, it is a complex endocrine disorder in which several genes are likely to play a part. Case-control studies of over 100 candidate genes have failed to re- veal a clear candidate locus (or loci) but recent genome-wide asso- ciation studies (GWAS) have proved more fruitful, albeit with some unexpected findings, which may lead to a better understanding of the aetiology of PCOS. A recently meta-analysis of the available GWAS studies has helped to clarify the genetic basis of PCOS. There was a similar pattern in the genetic architecture between the various diagnostic criteria, indicating a common genetic basis amongst the different diagnostic subtypes and suggesting a common aeti- ology despite heterogeneity of clinical and biochemical features. In addition, as in type 2 diabetes, the phenotype is modified by en- vironmental factors and obesity clearly exacerbates endocrine and metabolic dysfunction and is associated with more severe symptoms. A new International Guideline has been published which attempts to collate the various aspects of diagnosis and management of PCOS (https://www.monash.edu/medicine/sphpm/mchri/pcos/guideline). In so doing, it points to the relative paucity of large, randomized con- trolled trials in assessing therapeutic options.
Hypothalamus LH FSH FSH GnRH Oestradiol Ovary Blood Pituitary (GnRH) Gonadotrophin releasing hormone − + Fig. 13.6.1.4 Induction of ovulation in patients with hypothalamic amenorrhoea. Exogenous GnRH may be administered by pulsatile infusion pump, leading to restoration of gonadotropin secretion and allowing normal negative feedback regulation of LH and FSH by ovarian steroids, thus limiting the risk of multiple follicle development. An alternative strategy is to give gonadotropins by daily injection but the risk of hyperstimulation is greater than with GnRH. Normal Ovary Polycystic Ovary Growing follicle Preovulatory follicle Fig. 13.6.1.5 Ultrasound images of a normal and polycystic
ovary, and of a growing and a preovulatory follicle.

 Definition and diagnostic criteria The ‘classic’ definition of PCOS, that is, hyperandrogenism associated with chronic anovulation (in the absence of any confounding pituitary or adrenal disorders) is notable for its lack of reference to the ovarian morphology and yet almost all women who meet these criteria will have polycystic ovaries. In addition, polycystic ovaries can be found in women with symptoms of hyperandrogenism but who have regular menstrual cycles, as well as in those with anovulation but no evi- dence of androgen excess. A consensus meeting held in 2003 revised the diagnostic criteria allowing a more inclusive definition (Table 13.6.1.4). This revision has inevitably led to some controversy about definition of PCOS but there is ample evidence that both women with polycystic ovaries who present with hyperandrogenism but have regular cycles, and those with oestrogen-replete amenorrhoea or oligomenorrhoea but who have no features of androgen excess, simply have varying forms of the same underlying condition. Indeed, prelim- inary data from the ongoing GWAS studies, across various popula- tions of women with PCOS, support this notion. Endocrine features The

heterogeneity of the clinical features of PCOS extends to the endocrine abnormalities associated with it. As a result, specific endocrine indices are not a requirement for diagnosis, although measurement can be helpful to support it and, importantly, to ex- clude other conditions. Until the advent of widely available high- resolution ultrasound, the diagnosis of PCOS was usually based on a combination of biochemical and clinical features. Raised serum testosterone concentration is the most commonly found biochemical abnormality in PCOS, occurring in about 70% of cases. Free androgen index (FAI), calculated from total testosterone and sex hormone binding globulin (SHBG), has been found a useful marker by some clinicians. However, since SHBG is closely associ- ated with BMI and, more particularly, abdominal circumference, the increased FAI found in PCOS is, at least in part, a reflection of an in- creased abdominal adiposity which is characteristic of the syndrome. Serum concentrations of the weak androgen, androstenedione, are also elevated in PCOS. In practical terms, measuring serum testos- terone is usually preferable to androstenedione as the process is auto- mated in most clinical laboratories and therefore more cost-efficient. This is however some concern about the specificity and precision of many commonly available androgen assays, particularly in women, with an emphasis being placed on the use of gas chromatography with mass spectrometry or, at least, well validated immunoassays. In 10–20% of patients with PCOS, serum levels of the weak adrenal androgen, dehydroepiandrosterone sulphate (DHEAS) are also mod- estly elevated, suggesting that there may be, at least in some patients with PCOS, an adrenal contribution to increased circulating androgens. Among women with PCOS, clinical signs of hyperandrogenaemia (e.g. hirsutism) are associated with higher testosterone levels than those without. The presence or absence of features of hyperandrogenism, however, does not accurately predict serum androgen levels as clinical expression depends on the peripheral conversion of testosterone to its active metabolite, 5α-dihydrotestosterone (DHT) by 5α-reductase, as well as end-organ sensitivity (androgen receptor activity) (see section on hyperandrogenism). Obesity in PCOS is associated with higher free testosterone levels in comparison to lean counterparts and, in part, this reflects the lower SHBG levels found in the former group. In addition, obesity may have an independent effect on peripheral an- drogen metabolism since androsterone glucuronide levels, a marker for peripheral 5α-reductase activity, are raised in this group. Genetic factors may affect end-organ sensitivity: for example, PCOS occurs in the Chinese and Japanese, but hirsutism is relatively uncommon in these races. In contrast, hirsutism features commonly in women with PCOS from the Indian subcontinent. Women with PCOS tend to have higher LH levels compared to those with normal ovaries. The highest prevalence of elevated LH levels is in those with anovulatory menses or amenorrhoea but even in this group more than 40% will have normal LH. In contrast, FSH levels are normal but tend to be lower than in the normal early fol- licular phase. Many have cited a raised LH:FSH ratio (either 2.5:1 or 3:1) as a diagnostic feature of PCOS, but it is neither sensitive nor specific enough to be used as a reliable diagnostic criterion. Oestrogen levels in women with all variants of PCOS are normal. As discussed previously, this can be used to distinguish between oligo/amenorrhoeic women with PCOS and those with other causes of anovulation such as hypothalamic or pituitary disorders or ovarian failure. Plasma oestradiol levels in PCOS lie within the range normally seen in the early to mid-follicular phase of the menstrual cycle, but oestrone levels are typically higher than normal. This is probably due to the increased peripheral conversion of high circu- lating androstenedione to oestrone in adipose tissue. Hyperprolactinaemia has been described in association with PCOS, but this usually reflects spurious fluctuations in serum pro- lactin, probably occurs no more commonly than in the normal population and is rarely a persistent problem. Metabolic abnormalities Polycystic ovary syndrome is not just a reproductive disorder it is also associated with a characteristic metabolic abnormality, cen- tral to

which is peripheral insulin resistance and compensatory hyperinsulinaemia. Insulin resistance is independent of body weight but the difference between women with PCOS and controls is amplified with increasing body weight. Reduced insulin sensitivity is related to an abnormality in energy balance, specifically reduced postprandial thermogenesis, which may contribute to develop- ment of obesity. Interestingly, insulin resistance in PCOS appears to be confined to (or at least is most apparent in) the major sub- group of women who have both anovulation and hyperandrogenism (Table 13.6.1.5). Typically, women with PCOS have increased abdom- inal adiposity (and visceral fat accumulation) and this is correlated with insulin resistance. There is also an associated dyslipidaemia, characterized by lower than normal serum concentrations of Table 13.6.1.4 Diagnostic criteria for polycystic ovary syndrome (PCOS) according to National Institutes of Health (NIH) conference on PCOS 1990 and the joint ESHRE/ASRM consensus conference, Rotterdam 2003 NIH 1990a Rotterdam 2003b Chronic anovulation Oligo- and/or anovulation Clinical and/or biochemical signs of hyperandrogenism Clinical and/or biochemical signs of hyperandrogenism Polycystic ovaries a Both criteria needed; b 2 of 3 criteria required. Diagnosis, using either set of criteria, assumes that other aetiologies that may mimic PCOS (e.g. nonclassical 21-hydroxylase deficiency) have been excluded.

 high-density lipoprotein cholesterol (HDL-C) and elevated levels of low-density lipoprotein cholesterol (LDL-C). Although glucose toler- ance is often normal in these women, impaired glucose tolerance has been noted in 10–40% of young obese women with PCOS with frank diabetes in 5–10%. The defect in insulin action associated with PCOS appears to be secondary to a defect in postreceptor signal transduc- tion and shows subtle differences from that found in other insulin re- sistant states. The major defect associated with PCOS, independent of obesity, is within insulin signalling in classic insulin target tissues such as muscle. Suppression of hepatic gluconeogenesis is reduced, but only in obese PCOS women. In contrast, obesity alone has a smaller effect on the sensitivity of insulin-mediated glucose utilization but a greater effect on the rate of glucose utilization. There is some debate as to whether this insulin resistance in PCOS represents a primary defect in insulin action or whether it is secondary to hyperandrogenism and/or the result of increased truncal-abdominal fat. The interaction of insulin and androgens is complex. Experimental data suggest that androgens affect flux of free fatty acids from visceral fat deposits, which may, in turn, affect insulin sensitivity. However therapeutic reduction of serum androgen levels does not appear to im- prove insulin sensitivity. On the other hand, hyperinsulinaemia clearly affects androgen production. Insulin has gonadotropic activity and can influence ovarian steroidogenesis by both theca and granulosa cells by an interaction with LH. In addition, hyperinsulinaemia reduces hepatic production of SHBG and thereby raises levels of non-protein- bound (i.e. biologically available) testosterone. Reproductive consequences Polycystic ovary syndrome is by far the most common cause of anovulatory infertility, accounting for more than 75% of cases. Anovulation is the undoubtedly the principal reason for subfertility in women with polycystic ovaries but there has been some specu- lation that polycystic ovaries, in the absence of the syndrome, may contribute to problems with fertility. Polycystic ovaries are found more commonly than in the general population in infer- tile, ovulatory women with tubal disease (50%), in women whose partners have sperm dysfunction (53%) and in couples with unex- plained infertility (44%). Women with polycystic ovaries are also overrepresented among women with a history of recurrent miscar- riage (three or more consecutive miscarriages). However, the live birth rate, of ovulatory women with polycystic ovaries, after spon- taneous conception, is the same as that in a well-matched population of women with normal ovaries. Long-term consequences The

significance of PCOS for women’s health at a population level is increasingly being recognized. While the management of symptoms of PCOS such as infertility and hirsutism is important, consider- ation must also be given to management, and, if possible, prevention of long-term effects of the disorder. These include increased risk of developing endometrial cancer, and the consequences of metabolic abnormalities, namely diabetes and cardiovascular disease. Endometrial carcinoma. PCOS has been recognized as a risk factor for endometrial carcinoma since the 1950s and there are reports of the disease occurring in young (premenopausal) women with PCOS. In women with PCOS who have amenorrhoea or infrequent menses, the endometrium is exposed to prolonged stimulation with oestrogen in the absence of cyclical progesterone (so-called ‘unopposed’ oestrogen). This may lead to endometrial hyperplasia and, if untreated, to endometrial car- cinoma. Obesity adds to the risk of developing endometrial cancer by several interrelated intermediary factors including increased oes- trogen production, hyperinsulinaemia, and reduced serum SHBG. Gestational diabetes. The link between PCOS, insulin resistance and impaired glucose tolerance suggests that women with PCOS are at increased risk of developing both type 2 diabetes and gestational diabetes (GDM). The physiological insulin resistance of pregnancy adds to that in- trinsic to PCOS and may unmask impaired pancreatic β cell func- tion. The evidence for increased risk of GDM among women with PCOS is suggestive but not yet compelling. Most of the studies to date have been small and retrospective, and involve ethically mixed populations. Meta-analysis of these smallish studies suggested a 3-fold increase in risk of GDM in women with PCOS but a more recent prospective, multicentre study in the Netherlands found a prevalence of GDM in their PCOS population of 22% (against an expected population prevalence of around 5%). Type 2 diabetes mellitus. As indicated earlier, impaired glucose tolerance (IGT) and even frank diabetes are common in obese young women with PCOS. Longitudinal studies have been limited both in number and in duration of follow-up but those that are available indicate that the prevalence of both IGT and diabetes increase, as might be predicted, with age (and inevitably BMI). Likewise, population studies have been few, but the results sup- port the view that PCOS is a significant risk factor for development of type 2 diabetes. The relative risk is around twofold after adjustment for obesity but rises to 3–7-fold in obese women with PCOS. Cardiovascular risk. Polycystic ovary syndrome is associated with well-recognized risk factors for cardiovascular disease: namely obesity, insulin resistance, dyslipidaemia, diabetes, and (in some but not all studies) hyperten- sion. In addition, surrogate markers of cardiovascular disease have also been found to be abnormal. Endothelial function is impaired in young women with PCOS. Carotid artery intima–media wall thickness (associated with an adverse cardiovascular risk profile in middle-aged and elderly general populations) is increased in women with PCOS over the age of 45 years and carotid plaques are more common. Coronary artery calcification is a marker for coronary ath- erosclerosis and is also more common in women with PCOS than BMI-matched controls. Left ventricular mass index was found to be increased and diastolic dysfunction present in obese and nonobese young women with PCOS, suggesting a detrimental effect on the cardiovascular system, although this is yet to be confirmed. Table 13.6.1.5 Typical metabolic features of PCOS. Metabolic abnormalities are much more prevalent in women who have both anovulation and androgen excess and are exacerbated by obesity Metabolic features of PCOS Insulin resistance and hyperinsulinaemia Abnormal energy expenditure (reduced postprandial thermogenesis) Dyslipidaemia Impaired glucose tolerance

 It might be expected from the presence of multiple risk factors for cardiovascular disease that women with PCOS, especially if obese, would have an increased morbidity and mortality from the condition. There are few epidemiological studies and no

substantial longitudinal studies, but the data so far suggest that there are fewer cardiovascular events than would have been predicted from the cluster of risk fac- tors. The two largest studies give a similar odds ratio (1.5) for the risk of cardiovascular events. In both studies, the populations were under 60 years of age, so it remains possible that the relative risk of heart attacks (and stroke) will increase with age. An alternative explan- ation is that there are factors in women with PCOS that are protective against cardiovascular disease, for example, as a result of unopposed oestrogen or even raised androgen levels. Perhaps most importantly of all, it must be appreciated that the presence of risk factors does not prove the presence of the disease and that surrogate markers are not necessarily reliable predictors of outcome. Management of PCOS The management of PCOS is mainly targeted at relief of symptoms. Symptoms of androgen excess, including hirsutism, acne, or alo- pecia can be attenuated by use of antiandrogens, such as cyproterone acetate (CPA) and spironolactone (which, in the absence of CPA, is widely used in the United States). Flutamide is a pure antiandrogen (i.e. unlike, CPA, it has no progestogenic activity) but its place is less secure in management of symptoms of androgen excess because there are fewer studies to support its routine use and there have been reports of hepatic toxicity. Low-dose CPA or drospirenone (a derivative of spironolactone) may be conveniently combined with ethinyl oestradiol (co-cyprindiol or Dianette® and Yasmin®, respect- ively) and these preparations are particularly useful in those women with accompanying menstrual disturbance. They are also effective contraceptives. For those in whom oestrogen is contra-indicated, CPA or spironolactone can be given alone but nonhormonal contraception should be advised in those at risk of pregnancy because of the theoretical risk of feminization of a male fetus. Eflornithine inhibits the enzyme ornithine decarboxylase (ODC) which is involved in the production of the hair shaft. When applied topically, it can slow the growth of hair, although the effect can take 2 to 4 months to become apparent. Women often seek medical help with hirsutism when ‘beauty treatments’ such as waxing, plucking, electrolysis, and laser become inconvenient or too expensive. It is important to ensure a realistic expectation of treatment, which is that antiandrogens should be used as adjuncts, not replacements, to beauty treatments. In addition, hormone treatment may take 9 to 12 months to become fully effective: an improvement in hirsutism is often best judged by a reduced frequency of hair-removal treat- ment. Antiandrogen therapy is also effective for acne but, unfortu- nately, alopecia rarely improves with antiandrogen treatment and the objective here is to limit further hair loss. It is therefore im- portant to treat early signs of androgen-dependent hair loss. Anovulatory women with PCOS who wish to conceive usually re- spond to ovulation induction therapy (Fig. 13.6.1.6). The principle is to raise serum FSH levels to encourage development of a single, healthy dominant follicle (and therefore limit the risk of multiple pregnancy). The first-line treatment is the antioestrogen clomi- phene. Around 75–80% of women will ovulate in response to clomi- phene. In those who do not respond, or do not conceive after six or more ovulatory cycles, treatment with exogenous gonadotropin is appropriate. The modern approach is to start with a low dose of FSH and, if necessary, make small increments in dose to find the ‘threshold’ for development of a single dominant follicle. Even low- dose FSH treatment, requires close monitoring to reduce the risks of multiple pregnancy. An alternative to gonadotropin treatment is laparoscopic ovarian diathermy, a single, if invasive, procedure. However, surgery alone will result in ovulatory cycles in less than 50% of subjects and adjuvant clomiphene or FSH treatment is often required. In anovulatory women with PCOS who do not wish to conceive, regulation of menses can be ensured by treatment with a combined oral contraceptive or cyclical progestogen treatment. Because of the risk of endometrial hyperplasia or cancer, it is important to offer such treatment even in women with amenorrhoea or oligomenorrhoea who are not concerned

about lack of periods, In obese women with PCOS calorie restriction is not only de- sirable but also surprisingly effective in improving symptoms of PCOS, particularly menstrual pattern and fertility. Dietary restric- tion leading to merely a 5 to 10% reduction weight is associated with much improved ovarian function. Overweight and obese women re- spond poorly to induction of ovulation and from an obstetric view- point, the risks of GDM and pregnancy-related hypertension are increased. Weight reduction before fertility treatment, though never easy to achieve, is therefore an important aspect of management. Evidence from the Diabetes Prevention Program, a prospective study of men and women with IGT, suggests that calorie restric- tion, coupled with lifestyle changes (including increased exercise) will reduce the risk of conversion to diabetes. While there are, as yet, no such studies in women with PCOS, it is logical that such an approach will also reduce the chance of developing diabetes in this 'at risk' group. Hypothalamus LH FSH FSH antioestrogens (e.g. clomiphene) Oestradiol Ovary Blood Pituitary (GnRH) Gonadotrophin releasing hormone − + Fig. 13.6.1.6 Induction of ovulation in polycystic ovary syndrome. The treatment of first choice is the antioestrogen clomiphene which leads to elevation of serum FSH. If this is ineffective, exogenous FSH can be given by daily, low-dose injection.

 The Diabetes Prevention Program also showed that the biguanide, metformin—which has long been used for treatment of type 2 diabetes—was effective in reducing conversion from IGT to dia- betes (although significantly less so than diet and lifestyle changes). In recent years, metformin has been enthusiastically advocated for management of PCOS, even in the absence of IGT. A large number of publications have supported its use in fertility treatment (par- ticularly in combination with clomiphene), menstrual regulation, and management of hirsutism. However, there have been few large randomized controlled trials of metformin in management of PCOS, and those few adequately powered studies that have been performed to date have failed to support those claims. It remains to be seen whether metformin has a role in diabetes prevention in women with PCOS. Other causes of hyperandrogenism in women Hyperandrogenism, which, in this context, is defined as clinical evi- dence of androgen excess in women, is a common and distressing problem. Hyperandrogenism manifests itself as hirsutism (or ex- cess, unwanted male-pattern hair), persistent acne or androgenic alopecia (male-pattern balding). Although PCOS is the commonest cause of androgen excess, it is important to consider other possible diagnoses.

Physiology of androgen-dependent hair growth and androgen production in women During puberty, circulating androgen concentrations rise and the familiar pattern of androgen-dependent body (terminal) hair growth is seen. In normal, premenopausal women, the adrenal is the predominant source of androgens. Testosterone is the most important circulating androgen and is secreted by both ovaries and adrenals. But about 50% of circulating testosterone is derived by conversion from androstenedione (a weak androgen) in per- ipheral tissues such as skin and adipose. More than 90% of circu- lating testosterone is bound either to SHBG or albumin. Only the unbound (and possibly albumin-bound) testosterone is available to target tissues. Testosterone is further metabolized within the hair follicle to the more potent androgen, dihydrotestosterone (DHT) by the enzyme 5-α-reductase. Both testosterone and (with a higher affinity) DHT bind to specific androgen receptors within the hair follicle to affect growth of terminal hair. The biological effect of an- drogens may also be regulated at the level of the androgen receptor itself. Recent evidence suggests that heterogeneity of the androgen receptor is conferred by epigenetic modification of the androgen receptor gene and that these modifications are related to clinical in- dices of androgenicity. Causes of hirsutism The causes of hirsutism are summarized in Table 13.6.1.6. Hirsutism is most commonly caused by PCOS. It accounts for about 90% of cases, including those who might previously have been labelled as

having idiopathic hirsutism. However, hirsutism may be a mani- festation of other, much rarer but more serious, endocrine disorders such as Cushing syndrome and adrenal or ovarian tumours. Careful clinical evaluation is the key to differential diagnosis. Long-standing mild to moderate hirsutism, with or without menstrual disturbance is suggestive of PCOS (or idiopathic hirsutism) while a short history of increasing hirsutism in a previously nonhirsute subject should alert the physician to the possibility of alternative diagnoses. Hirsutism and menstrual disturbances are common presenting fea- tures in women with Cushing syndrome or androgen-secreting tu- mours. In the case of Cushing syndrome, the presence of additional features such as hypertension, easy bruising, and striae, help to make the diagnosis more likely. Hyperthecosis refers to the histological finding of islands of theca cells within dense ovarian stroma and is almost certainly a variant of PCOS. Its clinical presentation is indistinguishable from that of PCOS but it tends to be associated with severe hirsutism and there is often also cutaneous evidence of significant insulin resistance (acanthosis nigricans). Another well-recognized cause of hirsutism that may be diffi- cult to distinguish clinically from PCOS nonclassical (late onset) congenital adrenal hyperplasia (CAH) due to 21-hydroxylase de- ficiency. Such cases tend to present first during adolescence with symptoms of anovulation and androgen excess, but rarely can pre- sent in adulthood. Androgen-secreting ovarian and adrenal tumours are rare. Causes, diagnosis, and management of adrenal tumours are de- scribed elsewhere (Chapter 13.5.1). Ovarian tumours may be benign or (less commonly) malignant and are classified as ei- ther sex cord stromal tumours (Sertoli-Leydig cell tumours), or adrenal-like tumours (e.g. virilizing lipoid cell tumours, adrenal rest tumours). Investigation and diagnosis of hirsutism A guide to investigation of hirsutism is given in Table 13.6.1.7. Mild-moderate long-standing hirsutism in women with regular menses is very likely to be either idiopathic or, much more com- monly, associated with polycystic ovaries. Serum testosterone con-centrations are usually modestly elevated or within the normal range. It could be argued that no investigations are strictly necessary in this category of patients but measuring serum testosterone and determining ovarian morphology by pelvic ultrasound scan, means a specific diagnosis can be offered to the patient. The principal reason for measuring testosterone in women with hirsutism is to screen for the more serious causes of androgen excess that will require further investigation. It is not measured to diagnose hyperandrogenism since this is already manifested clinically as hirsutism. It is not ne- cessary to measure routinely androstenedione, SHBG, or free tes- tosterone. Some laboratories offer androstenedione as a reasonable alternative to testosterone assays.
Table 13.6.1.6 Causes of hirsutism Ovarian Polycystic ovary syndrome (>80%) Hyperthecosis (5–10%) Ovarian tumours (<1%) Adrenal Congenital adrenal hyperplasia (classical, 1%; nonclassical (late onset, 3%) Cushing syndrome (<1%) Adrenal tumours (<1%) Idiopathic With raised androgens (5%) Without raised androgens (7%)

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