Despite the probable benefits, there is substantial evidence to show that HRT is associated with an increased risk of cancer, particularly breast cancer (see Breast under Carcinogenicity, above), and some cardiovascular diseases such as stroke and venous thromboembolism (see Effects on the Cardiovascular System, above). It is now generally recommended by authorities, such as the UK CSM,[8] that the risk to benefit ratio of HRT is unfavourable for the prevention of osteoporosis as first-line therapy, and that it should not be used in this way for women over 50 years of age. HRT does, however, remain an option when other osteoporosis prevention therapies are unsuitable. Younger women who have experienced premature menopause may be given HRT for menopausal symptoms and to prevent osteoporosis until the age of 50, after which its use should be reviewed and considered a second-line choice.

Suggested minimum daily doses are 625 micrograms of oral conjugated oestrogens, 2 mg of oral estradiol or 50 micrograms transdermally, and 15 micrograms of oral ethinylestradiol; lower doses may also be effective,[9-15] and a transdermal patch supplying 14 micrograms of estradiol daily is licensed for the prevention of osteoporosis in the USA. Addition of a progestogen (required to prevent endometrial hyperplasia in women with a uterus) does not impair the beneficial effect of oestrogens on BMD, whether given cyclically or continuously,[16,17] and may provide a further reduction in risk of fractures.[18] Although current, long-term use of HRT can increase BMD and reduce fracture risk, unresolved issues are the duration of therapy required to prevent fractures in old age, and the ideal age to start therapy to obtain the maximum benefits to the bone with the minimum risk of breast cancer.[18-20]

Oestrogens may also be used in women to reduce the risk of corticosteroid-induced osteoporosis (see Effects on Bones and Joints, p.1491).

1. Cauley JA, *et al.* Effects of hormone replacement therapy on clinical fractures and height loss: the Heart and Estrogen/Progestin Replacement Study (HERS). *Am J Med* 2001; **110:** 442–50.
2. Hulley S, *et al.* Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288:** 58–66.
3. Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001; **285:** 2891–7.
4. Cauley JA, *et al.* Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003; **290:** 1729–38.
5. Banks E, *et al.* Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA* 2004; **291:** 2212–20.
6. Greendale GA, *et al.* Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. *Arch Intern Med* 2002; **162:** 665–72.
7. Yates J, *et al.* Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. *Obstet Gynecol* 2004; **103:** 440–6.
8. MHRA. Further advice on safety of HRT: risk:benefit unfavourable for first-line use in prevention of osteoporosis—Epinet message from Professor G Duff, Chairman of CSM (issued December 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019496.pdf (accessed 26/08/08)
9. Recker RR, *et al.* The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women: a randomized, controlled trial. *Ann Intern Med* 1999; **130:** 897–904.
10. Prestwood KM, *et al.* The effect of low dose micronized 17β-estradiol on bone turnover, sex hormone levels, and side effects in older women: a randomized, double blind, placebo-controlled study. *J Clin Endocrinol Metab* 2000; **85:** 4462–9.
11. Bjarnason NH, *et al.* Low doses of estradiol in combination with gestodene to prevent early postmenopausal bone loss. *Am J Obstet Gynecol* 2000; **183:** 550–60.
12. Lees B, Stevenson JC. The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17β and dydrogesterone. *Osteoporosis Int* 2001; **12:** 251–8.
13. Lindsay R, *et al.* Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA* 2002; **287:** 2668–76.
14. Prestwood KM, *et al.* Ultralow-dose micronized 17β-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. *JAMA* 2003; **290:** 1042–8.
15. Lindsay R, *et al.* Bone response to treatment with lower doses of conjugated estrogens with and without medroxyprogesterone acetate in early postmenopausal women. *Osteoporosis Int* 2005; **16:** 372–9.
16. The Writing Group for the PEPI trial. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. *JAMA* 1996; **276:** 1389–96.
17. Speroff L, *et al.* The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART Study): a randomized controlled trial. *JAMA* 1996; **276:** 1397–1403.
18. Michaëlsson K, *et al.* Hormone replacement therapy and risk of hip fracture: population based case-control study. *BMJ* 1998; **316:** 1858–63.
19. Schneider DL, *et al.* Timing of postmenopausal estrogen for optimal bone mineral density: the Rancho Bernardo study. *JAMA* 1997; **277:** 543–7.
20. Cauley JA, *et al.* Timing of estrogen replacement therapy for optimal osteoporosis prevention. *J Clin Endocrinol Metab* 2001; **86:** 5700–5.

Urinary incontinence. Urinary incontinence (p.2180) may be one of a number of acute symptoms associated with a decline in oestrogen levels at the menopause (see Menopausal Disorders, above). Studies[1,2] suggest that oestrogens used with alpha-adrenoceptor agonists are effective in the management of female stress incontinence and this combination has been advocated for use in postmenopausal patients with mild symptoms. Unfortunately addition of a progestogen to treatment to reduce the risk of endometrial carcinoma in women with an intact uterus might exacerbate the incontinence.[3] The value of oestrogens used without an alpha-adrenoceptor agonist in urinary incontinence is less clear. One study[4] reported that oestrogen therapy and pelvic floor exercises for 18 months was more effective than exercises alone in women with mild stress incontinence. However, a placebo-controlled study[5] found no improvement after 6 months of oestrogen therapy.

Some consider that oestrogens may be of use for symptoms of urgency, frequency, and nocturia in postmenopausal patients with urge incontinence, particularly if given locally;[6] it has been suggested that hypoestrogenism may reduce the sensory threshold of the bladder.[7] A meta-analysis of 23 studies concluded that oestrogen therapy subjectively improved urinary incontinence in postmenopausal women but many of the studies examined were considered to be deficient in some respect.[8] Later well-designed studies[9,10] of women with stress, urge, or mixed incontinence found that HRT did not improve, or even worsened, measures of incontinence, although there was the possibility that concomitant progestogen therapy might have affected efficacy. Furthermore, the placebo-controlled Women's Health Initiative[11] found that both oestrogen alone and combination HRT increased the overall risk of developing stress, urge, or mixed incontinence, and worsened incontinence in women who were symptomatic before starting HRT. Another placebo-controlled study[12] also found that combination HRT increased the risk of developing stress or urge incontinence, and the large Nurses' Health Study cohort reported[13] that the current use of HRT increased the risk of developing urinary incontinence.

1. Walter S, *et al.* Stress urinary incontinence in postmenopausal women treated with oral estrogen (estriol) and an alpha-adrenoceptor-stimulating agent (phenylpropanolamine): a randomized double-blind placebo-controlled study. *Int Urogynecol J* 1990; **1:** 74–9.
2. Hilton P, *et al.* Oral and intravaginal estrogens alone and in combination with alpha-adrenergic stimulation in genuine stress incontinence. *Int Urogynecol J* 1990; **1:** 80–6.
3. Benness C, *et al.* Do progestogens exacerbate urinary incontinence in women on HRT? *Neurourol Urodyn* 1991; **10:** 316–17.
4. Ishiko O, *et al.* Hormone replacement therapy plus pelvic floor muscle exercise for postmenopausal stress incontinence: a randomized, controlled trial. *J Reprod Med* 2001; **46:** 213–20.
5. Jackson S, *et al.* The effect of oestrogen supplementation on post-menopausal urinary stress incontinence: a double-blind placebo-controlled trial. *Br J Obstet Gynaecol* 1999; **106:** 711–18.
6. Cardozo L, *et al.* A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. *Acta Obstet Gynecol Scand* 2004; **83:** 892–7.
7. Fantl JA, *et al.* Postmenopausal urinary incontinence: comparison between non-estrogen-supplemented and estrogen-supplemented women. *Obstet Gynecol* 1988; **71:** 823–8.
8. Fantl JA *et al.* Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis: first report of the hormones and urogenital therapy committee. *Obstet Gynecol* 1994; **83:** 12–18.
9. Fantl JA, *et al.* Efficacy of estrogen supplementation in the treatment of urinary incontinence. *Obstet Gynecol* 1996; **88:** 745–9.
10. Grady D, *et al.* Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. *Obstet Gynecol* 2001; **97:** 116–20.
11. Hendrix SL, *et al.* Effects of estrogen with and without progestin on urinary incontinence. *JAMA* 2005; **293:** 935–48.
12. Steinauer JE, *et al.* The Heart and Estrogen/Progestin Replacement Study Research Group. Postmenopausal hormone therapy: does it cause incontinence? *Obstet Gynecol* 2005; **106:** 940–5.
13. Grodstein F, *et al.* Postmenopausal hormone therapy and risk of developing urinary incontinence. *Obstet Gynecol* 2004; **103:** 254–60.

Gonad-regulating Hormones

The Hypothalamic-Pituitary-Gonadal Axis

The regulation of sexual function involves the so-called hypothalamic-pituitary-gonadal axis.

The pituitary gland or hypophysis is composed in humans of 2 parts, the anterior lobe or adenohypophysis, and the posterior lobe (neurohypophysis) and neural stalk, above which lies the hypothalamus. Both parts of the pituitary secrete hormones: posterior pituitary hormones are synthesised in the hypothalamus and transported down nerve fibres to the pituitary where they are stored until required, whereas anterior pituitary hormones are synthesised *in situ* by specialised cells, but are subject to complex hormonal control by hypothalamic regulatory hormones and target organ hormones, as well as excitatory and inhibitory impulses from the brain. These interacting systems are collectively known as the hypothalamic-pituitary-endocrine axes.

The anterior pituitary hormones follicle-stimulating hormone (FSH) and luteinising hormone (LH) are collectively known as **gonadotrophic hormones** or gonadotrophins. They are glycoproteins secreted by specialised pituitary cells (gonadotropes) that stimulate gonadal function and sex hormone production. In men, LH stimulates the synthesis of testosterone and other androgens, while in women, FSH and LH regulate production of oestradiol and synthesis of progesterone in a complex and interacting manner. A third substance with gonadotrophic (primarily luteinising) actions, chorionic gonadotrophin, is secreted by the placenta.

The synthesis and secretion of pituitary gonadotrophic hormones is in turn stimulated by a hypothalamic releasing hormone, **gonadotrophin-releasing hormone** (GnRH). In post-pubertal subjects, GnRH is secreted from the hypothalamus at regular intervals determined by an internal 'clock' or neuronal pulse generator in the arcuate nucleus, and enters the blood of the portal vascular system that links the hypothalamus to the anterior pituitary. This results in pulsatile release of the gonadotrophic hormones, which is essential for normal gonadal function. More prolonged and continuous exposure to GnRH leads to desensitisation and downregulation of its receptors on pituitary gonadotropes, and hence, after an initial surge, to suppression of gonadotrophic hormone secretion.

The sex hormones themselves produce negative feedback effects at both hypothalamic and pituitary levels. In general, both oestrogen and progesterone reduce the amplitude (i.e. the amount) of gonadotrophic hormone released; progesterone also reduces the frequency of the pulses. Testosterone is thought to act by conversion to oestrogen via aromatase, although it also has some direct action. The gonads also produce a hormone, inhibin, that selectively inhibits FSH secretion from the pituitary without affecting LH, and its biological opposite, activin, which stimulates pituitary FSH secretion.

Types of Gonad-regulating Hormone

Gonad-regulating hormones in clinical use may be divided into 3 major groups.

- Endogenous follicle-stimulating and luteinising hormones are available from urinary sources as human menopausal gonadotrophins or menotrophin (p.2109) and as urofollitropin (p.2136), and in recombinant forms such as follitropins alfa and beta (p.2104) and lutropin alfa (p.2112). Chorionic gonadotrophin and its recombinant form choriogonadotropin alfa (p.2085) are also used.
- The hypothalamic releasing hormone gonadorelin (p.2106), and its longer-acting analogues such as buserelin (p.2083), deslorelin (p.2093), goserelin (p.2108), histrelin (p.2109), leuprorelin (p.2111), nafarelin (p.2117), and triptorelin (p.2135) are widely used to stimulate or inhibit the hypothalamic-pituitary-gonadal axis.
- More recently, direct gonadotrophin-releasing hormone antagonists have become available, such as abarelix (p.2081), cetrorelix (p.2084), and ganirelix (p.2105).

Use of Gonad-regulating Hormones

The gonad-regulating hormones play an important role in the management of a number of endocrine disorders, as discussed in the reviews below and elsewhere in this chapter. They also play an important role in the management of endocrine-sensitive malignant neoplasms (see p.643).

Amenorrhoea

Amenorrhoea is the absence of menstruation: a break in menstruation of 6 months or more is considered pathological in an adult woman who is not pregnant, lactating, or menopausal. Amenorrhoea occurring from the time of puberty is known as primary, while amenorrhoea developing later in life is referred to as secondary. Pathological amenorrhoea is usually associated with infertility (see also below). Hirsutism (p.2089) may also be present.

The causes of amenorrhoea (or oligomenorrhoea—infrequent and erratic periods) are most often ovarian or hypothalamic/pituitary in origin. Ovarian causes include failure of normal gonadal development, as in Turner's syndrome (below); premature ovarian failure including that due to trauma, drugs, radiotherapy, or autoimmunity; and conditions such as the polycystic ovary syndrome (below). Hypothalamic or pituitary causes include reduced production of gonadotrophins due to inadequate nutrition, excessive exercise, or pituitary trauma (see also Hypogonadism, below); or excess prolactin production (see Hyperprolactinaemia, below). Other causes, including adrenal disorders, thyroid disorders, abnormalities of the vagina or uterus, or testicular feminisation, may be found rarely.

The management of amenorrhoea essentially involves the identification of any underlying disorder and its correction, if possible. When the cause cannot be corrected, oestrogen replacement therapy, usually in the form of an oral contraceptive, is appropriate to minimise the consequences of long-term oestrogen deficiency.

References.

1. McIver B, *et al.* Evaluation and management of amenorrhea. *Mayo Clin Proc* 1997; **72:** 1161–9.
2. Baird DT. Amenorrhoea. *Lancet* 1997; **350:** 275–9.
3. Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril* 2006; **86** (issue 5 suppl 1): S148–S155.

Cryptorchidism

The testes are formed within the abdomen and subsequently descend the inguinal canal to the scrotum. Failure of the testes to descend (cryptorchidism) occurs in about 3 to 6% of newborn males but in many the testes descend during the first year of life decreasing the prevalence to about 1%. In children with cryptorchidism, pathological testicular damage has been noted by the age of 1 year, and may result in subsequent infertility; cryptorchidism also significantly increases the risk of testicular cancer. Abnormalities of the testes and anatomical abnormalities such as inguinal hernia may contribute to maldescent, and both primary testicular disease and gonadotrophin deficiency may be associated with cryptorchidism. For discussions of Hypogonadism and Infertility, see below. Cryptorchidism should be distinguished from retractile testes in which the testes develop normally and for which treatment is usually not required.

Although cryptorchidism is common, there is no consensus on the best treatment: surgery is commonly used in the USA whereas primary hormonal treatment is more popular in Europe.[1,2]

Surgery is successful in almost all cases, and is usually undertaken at around 1 year of age.[1,2] Primary hormonal therapy generally uses chorionic gonadotrophin or a gonadorelin analogue to stimulate androgen production. Success rates vary but reports are difficult to compare because of differences in patient age and treatment regimens, and the possible inclusion of retractile testes. Systematic reviews[3,4] suggest that gonadorelin and chorionic gonadotrophin are more effective than placebo with a success rate of about 20% overall, although this may be considerably lower if care is taken to exclude retractile testes. The lower the position of the undescended testis, the more likely benefit from hormonal therapy appears to be.[3,5] Treatment may also be less successful as boys grow older, and treatment before 12 to 18 months[6] or 2 years of age[4] has been recommended. Some reports suggest that results may be improved by combined therapy with gonadorelin and chorionic gonadotrophin,[7] but others have found no advantage over single drug therapy.[8,9] Surgery is used second-line when hormonal treatment is unsuccessful. There is some suggestion that medical treatment given either before or after surgery can improve the patient's fertility index, a predictor of future fertility.[6] Chorionic gonadotrophin may also be useful as an adjuvant before surgery, in order to cause a non-palpable testis to become palpable;[10] however, changes suggestive of inflammation in the testis have been reported after such treatment.[5]

Even after successful treatment, however, there may still be impaired fertility. Similarly, the risk of testicular cancer is not necessarily reduced, but orchidopexy does enable early detection and all patients should be monitored.[1,2]

1. Brucker-Davis F, *et al.* Update on cryptorchidism: endocrine, environmental and therapeutic aspects. *J Endocrinol Invest* 2003; **26:** 575–87.
2. Kolon TF, *et al.* Cryptorchidism: diagnosis, treatment, and long-term prognosis. *Urol Clin North Am* 2004; **31:** 469–80.
3. Pyörälä S, *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab* 1995; **80:** 2795–9.
4. Henna MR, *et al.* Hormonal cryptorchidism therapy: systematic review with metanalysis of randomized clinical trials. *Pediatr Surg Int* 2004; **20:** 357–9.
5. Kaleva M, *et al.* Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. *Int J Androl* 1996; **19:** 293–8.
6. Tekgül S, *et al.* European Society for Paediatric Urology, European Association of Urology. Guidelines on paediatric urology (issued March 2008). Available at: http://www.uroweb.org/fileadmin/user_upload/Guidelines/Paediatric%20Urology.pdf (accessed 31/03/08)
7. Giannopoulos MF, *et al.* 13 Year's experience with the combined hormonal therapy of cryptorchidism. *Horm Res* 2001; **55:** 33–7.
8. Bertelloni S, *et al.* Hormonal treatment for unilateral inguinal testis: comparison of four different treatments. *Horm Res* 2001; **55:** 236–9.
9. Esposito C, *et al.* Comparison of five different hormonal treatment protocols for children with cryptorchidism. *Scand J Urol Nephrol* 2003; **37:** 246–9.
10. Polascik TJ, *et al.* Reappraisal of the role of human chorionic gonadotropin in the diagnosis and treatment of the nonpalpable testis: a 10 year-old experience. *J Urol (Baltimore)* 1996; **156:** 804–6.

Delayed puberty

The onset of puberty is associated with an increase in the secretion of luteinising hormone. There is a subsequent increase in concentrations of sex hormones, the development of secondary sexual characteristics, and an associated growth spurt. Delayed puberty is diagnosed when there is no breast development by 13.4 years of age in girls, and no testicular enlargement by 14 in boys. In addition to the various causes of hypogonadism (see below), some of which may be difficult to diagnose, severe systemic illness such as asthma or diabetes, or hypothyroidism, may cause delay in sexual maturation. Where no apparent cause can be found a family history of delayed maturation may suggest constitutional delayed puberty, in which normal pubertal development can eventually be expected.

Where pubertal delay is secondary to some other condition appropriate management of the precipitating cause is required. In constitutional delayed puberty small doses of oestrogens in girls, or androgens (such as oxandrolone or a testosterone ester) in boys, may be given to promote growth and sexual development if psychological problems are apparent. Care is required as overly aggressive therapy with sex hormones may lead to premature closure of the epiphyses and compromise final adult height. Treatment should be interrupted periodically to see if spontaneous pubertal development has begun. The use of chorionic gonadotrophin or a gonadorelin analogue has no advantage in such patients, although they have a role in hypogonadotrophic hypogonadism, which may be difficult to distinguish from constitutional delay.

References.

1. De Luca F, *et al.* Management of puberty in constitutional delay of growth and puberty. *J Pediatr Endocrinol Metab* 2001; **14** (suppl): 953–7.
2. Traggiai C, Stanhope R. Delayed puberty. *Best Pract Res Clin Endocrinol Metab* 2002; **16:** 139–51.

Endometriosis

Gonadorelin analogues are used in the management of endometriosis (see p.2091) but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; 'add-back' therapy, with concomitant hormone replacement, can be used to prevent this.

Hyperprolactinaemia

Hyperprolactinaemia is a condition of elevated circulating prolactin concentrations. It occurs for physiological reasons in pregnancy or after mechanical stimulation of the nipple, as in suckling. However, hyperprolactinaemia may also be an adverse effect of drugs that inhibit dopaminergic function, such as antipsychotics and metoclopramide; other drugs causing hyperprolactinaemia include opioid analgesics, methyldopa, reserpine, oestrogens, SSRIs, and verapamil. Furthermore, pathological hyperprolactinaemia may be associated with prolactin-secreting pituitary adenomas (prolactinomas), damage to the pituitary stalk or hypothalamus (including that caused by non-secreting tumours), or trauma to the chest wall; it may also be associated with disorders such as Cushing's syndrome or hypothyroidism. Prolactinomas are amongst the commonest pathological causes, and so-called idiopathic hyperprolactinaemia, in which no apparent cause is found, may in fact represent undetected microadenoma.

The consequences of hyperprolactinaemia include suppression of ovarian function in women, leading to erratic cycles or amenorrhoea, and infertility (see also above and below respectively); in men, in whom the condition is less common, reduced gonadotrophin production leads to testosterone deficiency, diminished libido, and impotence. Both sexes may develop unwanted milk flow (galactorrhoea), although this also requires the presence of oestrogens; men may rarely develop gynaecomastia (p.2092) due to the change in oestrogen/androgen balance.

Management of hyperprolactinaemia depends on its cause. Pathological hyperprolactinaemia must be distinguished from physiological, and where it is secondary to another disease this should be managed appropriately; any drug thought likely to be causative should be withdrawn if possible. Some patients are asymptomatic, or are untroubled by their symptoms; whether such patients should be treated has been a matter of some controversy, although the risk of osteoporosis in women with prolonged suppression of ovarian function has been cited as a reason for such treatment.[1]

In many cases hyperprolactinaemia will be secondary to a prolactinoma. These are generally classified as microadenomas (less than 10 mm in size) or macroadenomas (over 10 mm in size); macroadenomas are often associated with prolactin concentrations more than 10 times the normal upper limit and their rapid expansion may result in visual defects and headache. Initially a course of treatment with a dopamine agonist such as bromocriptine, while rarely curative, is extremely effective in controlling hyperprolactinaemia and restoring gonadal function.[2,3] Surgical removal is now rarely indicated, although transsphenoidal decompression may be necessary for macroadenomas despite bromocriptine therapy, and ultimately radiotherapy may also be required.

The most extensively used dopamine agonist is bromocriptine; it decreases prolactin secretion and reduces tumour size in the majority of patients.[2] There are reports of maintained normoprolactinaemia and reduced tumour size when bromocriptine has been withdrawn after about 2 to 4 years of treatment.[4] However, this occurs in only a minority of patients, and macroadenomas in particular can re-expand, sometimes rapidly, when treatment is stopped.[2] It has been suggested[3] that when the prolactin concentration has been normal for 2 years and the tumour has decreased by at least 50%, the dose of bromocriptine can be gradually reduced, with close follow-up to detect tumour enlargement. The short half-life and the adverse effects of bromocriptine may pose problems, although depot formulations can minimise these. Giving oral prednisolone with intramuscular depot bromocriptine has been reported to reduce the incidence of adverse effects.[5]

Treatment of hyperprolactinaemia restores ovulation in the majority of female patients. In those who become pregnant it is generally advised that fetal exposure to the dopamine agonist should be as short as possible, and therefore stopped when pregnancy is confirmed. Bromocriptine is the drug of choice for patients who are planning pregnancy, because most experience exists with its use compared with other dopamine agonists. The hyperoestrogenic state of pregnancy itself can stimulate prolactinoma growth and patients must be carefully monitored throughout gestation. If symptomatic tumour growth occurs, bromocriptine may be restarted, which is probably less harmful to the mother and fetus than surgery. Surgical debulking before pregnancy has been advocated by some, but may not prevent symptomatic tumour enlargement during pregnancy.[2,6]

Alternative dopaminergic treatments include cabergoline and quinagolide.[2,7] Cabergoline appears to be more effective, and better tolerated, than bromocriptine, and can also be effective in patients who do not respond to bromocriptine. It is considered by some to be a first-line alternative, although bromocriptine is favoured in women who wish to become pregnant. Quinagolide appears to be of similar efficacy to bromocriptine, and may be useful in patients intolerant of or unresponsive to other drugs. Pergolide has also been tried, with similar efficacy to bromocriptine, but it is not licensed for such use.

1. Sanfilippo JS. Implications of not treating hyperprolactinemia. *J Reprod Med* 1999; **44:** 1111–15.
2. Molitch ME. Medical management of prolactin-secreting pituitary adenomas. *Pituitary* 2002; **5:** 55–65.
3. Schlechte JA. Prolactinoma. *N Engl J Med* 2003; **349:** 2035–41.
4. Passos VQ, *et al.* Long-term follow-up of prolactinomas: normoprolactinemia after bromocriptine withdrawal. *J Clin Endocrinol Metab* 2002; **87:** 3578–82.
5. Jenkins PJ, *et al.* Oral prednisolone supplement abolishes the acute adverse effects following initiation of depot bromocriptine therapy. *Clin Endocrinol (Oxf)* 1996; **45:** 447–51.
6. Randeva HS, *et al.* Prolactinoma and pregnancy. *Br J Obstet Gynaecol* 2000; **107:** 1064–8.
7. Bankowski BJ, Zacur HA. Dopamine agonist therapy for hyperprolactinemia. *Clin Obstet Gynecol* 2003; **46:** 349–62.

Hypogonadism

Hypogonadism (decreased or absent gonadal function) may occur in both men and women, and may be either primary, due to some dysfunction of the gonads themselves, or secondary, due to hypopituitarism or some other cause of decreased gonadotrophic stimulation.

Primary ovarian dysfunction may be due to failure of the ovaries to form normally, as in Turner's syndrome (see below), or their degeneration before puberty; there may be premature failure, effectively an early menopause, due to low initial follicle numbers or to destruction of follicles by autoantibodies, chemotherapy, radiotherapy, infection, or trauma. Primary testicular dysfunction may be due to congenital disorders such as Klinefelter's syndrome (associated with an XXY chromosome constitution); the effects of chemotherapy, radiotherapy, infections (particularly mumps), or trauma; and a few other conditions such as testicular degeneration.

Secondary hypogonadism may be due to general hypopituitarism, or to a specific deficiency of gonadotrophin production, or gonadorelin production. Kallmann's syndrome is a congenital disorder of hypogonadotrophic hypogonadism due to gonadorelin deficiency associated with anosmia or hyposmia. The causes of pituitary or hypothalamic failure include neoplasms, radiotherapy to the head and neck, trauma, or infiltrative granulomatous diseases such as tuberculosis. Gonadotrophin production may also be suppressed by various drugs (notably exogenous sex steroids and continuous, rather than pulsatile, use of gonadorelin analogues), by weight loss or inadequate nutrition, by excessive exercise, by severe systemic illness, and by hyperprolactinaemia (see above).

The fundamental treatment for primary hypogonadism is replacement therapy with sex hormones to produce appropriate sexual development and activity and counteract effects such as osteoporosis, but fertility cannot usually be restored. In prepubertal children, the induction of secondary sexual characteristics must be balanced against a possible reduction in final height due to premature closure of the bone epiphyses. Women are generally given an oestrogen with a progestogen, and men are treated with androgens, often in the form of a long-acting testosterone

ester such as the cipionate or enantate given intramuscularly. Transdermal testosterone is also effective.

The cause of secondary hypogonadism should be determined and managed appropriately if possible. In some cases this may be adequate to restore gonadal function but in other cases sex hormone replacement therapy as in primary hypogonadism will be required. Where there is no fundamental defect in gonadal function the possibility of using a gonadotrophic hormone or stimulating the release of gonadotrophins also exists. In general, however, such therapy is often reserved for attempts to restore fertility (see under Infertility, below), since it is inconvenient and expensive.

Further references.

1. Silveira LFG, *et al.* Hypogonadotropic hypogonadism. *Semin Reprod Med* 2002; **20:** 327–38.
2. AACE Hypogonadism Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update. *Endocr Pract* 2002; **8:** 439–56. Also available at: http://www.aace.com/pub/pdf/guidelines/hypogonadism.pdf (accessed 05/07/06)
3. Lanfranco F, *et al.* Klinefelter's syndrome. *Lancet* 2004; **364:** 273–83.

Infertility

Although about one couple in 6 may experience sufficient difficulty in conceiving children to seek medical help, most are subfertile rather than infertile, and may eventually conceive, with or without treatment. A number of possible treatments are available, but which is used depends upon the cause of the problem. Reduced fertility can have its origins in the male or the female partner or may be due to a combination of factors from both.

The most obvious cause of infertility is a failure of either ovulation in the female or spermatogenesis in the male. Such failures may be due to damage or abnormal formation of the gonads, a failure of hypothalamic/pituitary stimulation, abnormal feedback as in the polycystic ovary syndrome, or suppression of gonadal function as in hyperprolactinaemia. These conditions and their management are briefly discussed under Hypogonadism (above), Polycystic Ovary Syndrome (PCOS; below), and Hyperprolactinaemia (above).

Female factors. The primary problem in about 20% of infertile women is ovulatory dysfunction, and most of these women will have PCOS. *Clomifene* is often used first-line to stimulate ovulation in women with hypothalamic dysfunction, as in PCOS,[1-4] and has been reported to produce ovulation in about 70% of anovulatory women. Women with PCOS who do not respond to clomifene may be treated with ovarian drilling (laparoscopic diathermy).[2,4] Those who do ovulate with clomifene but have not become pregnant within 6 months may be offered intra-uterine insemination in addition to clomifene.[4] In overweight women with PCOS, metformin may be added when clomifene alone has not been effective.[1-4] The addition of a mid-cycle injection of chorionic gonadotrophin has also been tried for women who fail to ovulate with clomifene,[1] and to define the optimal time for intra-uterine insemination,[2] but such a regimen has not been proven to be better. Some women with clomifene-resistant anovulation may benefit from the sequential use of clomifene and a gonadotrophin that has follicle-stimulating activity.[2] In women with elevated dehydroepiandrosterone concentrations, the addition of a corticosteroid to clomifene may improve the ovulation rate.[1,2] Because of concerns about a possibly increased risk of ovarian cancer, opinion varies as to the maximum number of cycles for which clomifene should be used, but is usually either 6 or 12 cycles (see Carcinogenicity, p.2086). *Tamoxifen* is an alternative in those who cannot tolerate clomifene.[3,4] Aromatase inhibitors such as *letrozole* have also been tried, and seem to be at least as effective as clomifene in inducing ovulation,[5] although concerns about the potential for maternal or fetal toxicity remain to be assuaged.

Gonadotrophins with follicle-stimulating activity can be given directly to women with PCOS who have not ovulated with clomifene or tamoxifen; human menopausal gonadotrophin, urofollitropin, and recombinant follicle-stimulating hormone are considered to be equally effective.[4] Women with hypothalamic anovulation or hypogonadotrophic hypogonadism generally require gonadotrophins that also have luteinising hormone activity, because of low endogenous levels.[4,6] There is growing interest in the use of recombinant luteinising hormone in these patients.[6] Various regimens have been used but in general, follicle-stimulating hormone is given until a dominant follicle is suitably mature, and then chorionic gonadotrophin is given to trigger ovulation and provide luteal support.[6] The risks of ovarian hyperstimulation syndrome and multiple pregnancies are considerable however, particularly in PCOS, and close monitoring is mandatory using ovarian ultrasound to assess follicle development.[3,4]

Another method used for anovulation is pulsatile *gonadorelin*[4] (gonadotrophin-releasing hormone) or its analogues. It is primarily indicated in women with hypothalamic causes of anovulation; it is less effective in women with PCOS than in hypogonadotrophic patients.

Where anovulation is secondary to hyperprolactinaemia treatment with dopamine agonists such as bromocriptine can restore fertility (see Hyperprolactinaemia, above).

Where infertility is due to obstruction of the fallopian tubes or intra-uterine adhesions, surgery may be effective for some women.[4] Where infection is the cause, appropriate anti-infective agents may be useful. (See also under Pelvic Inflammatory Disease, p.184.)

Endometriosis (p.2091) is another important cause of infertility in women, although the reason for the association is not fully understood. Medical treatment of endometriosis does not enhance fertility, although conservative surgery may do so.[4]

In the absence of the above disorders and when infertility is otherwise unexplained the UK guidelines[4] indicate that treatment with clomifene should be offered.

Various other drugs have been used, on a more or less empirical basis. Growth hormone or one of its analogues has been used as an adjunct to ovarian stimulation with gonadotrophins but is not considered to improve pregnancy rates.[4]

Assisted reproduction may be considered when other methods fail. IVF is the most commonly used technique, in which oocytes are retrieved from the ovaries, fertilised *in vitro*, and resulting embryos are selected for transfer to the uterus. Less common techniques include transfer into a fallopian tube of gametes (an unfertilised egg and sperm) or a zygote (fertilised egg). Unlike ovulation induction described above, assisted reproduction techniques intentionally use ovarian hyperstimulation regimens to produce multiple oocytes for retrieval; women are therefore at risk of the ovarian hyperstimulation syndrome and should be monitored appropriately. Women with risk factors for ovarian hyperstimulation syndrome, such as those with PCOS, should not be given chorionic gonadotrophin for oocyte maturation or luteal support.[4] The most commonly used regimens are the 'long protocols' in which a gonadorelin agonist is started in the mid-luteal phase of the menstrual cycle to desensitise the pituitary and prevent a premature surge of luteinising hormone. When pituitary and ovulation suppression has been achieved, gonadotrophins (human menopausal gonadotrophins or follicle-stimulating hormone) are given to stimulate follicle production. At the appropriate stage of follicular development, a single dose of chorionic gonadotrophin is given to trigger ovulation. These 'long protocols' appear to give better results than short ('flare-up') or ultrashort regimens, in which gonadorelin agonists are given for less time, although short regimens may be useful in poor responders.[6] Meta-analysis indicates that recombinant follicle-stimulating hormone, urofollitropin, and human menopausal gonadotrophins are equally effective.[4] *Gonadorelin antagonists*, such as cetrorelix and ganirelix, have been used as an alternative to gonadorelin agonists. Pituitary desensitisation occurs more rapidly and shorter treatment regimens are used, but they may be associated with reduced pregnancy rates.[4,6,7] *Progesterone* is the preferred drug for luteal support for IVF procedures because of the increased likelihood of ovarian hyperstimulation syndrome with chorionic gonadotrophin.[4]

Male factors. Impaired male fertility may result from urogenital abnormalities, infections of the genital tract, increased scrotal temperature associated with varicocele, endocrine disturbances, genetic abnormalities, and immunological factors, but around 70% of cases may be idiopathic, where no causal factor is found.[8] Some forms of obstructive azoospermia can be corrected surgically. Varicocele repair with surgery or percutaneous embolisation may be considered in some men but the effects on fertility outcome are unclear.[8-10]

In men with hypogonadotrophic hypogonadism, replacement therapy with a gonadotrophin that has luteinising hormone activity, such as chorionic gonadotrophin, is given to stimulate testosterone production. Menopausal gonadotrophins, or the more specific follicle-stimulating hormone, are then added to stimulate spermatogenesis.[8,9] Spermatozoa may appear in the ejaculate after about 6 to 9 months of treatment, but may take considerably longer in some men.[9] Pulsatile gonadorelin may restore gonadotrophin secretion and correct infertility in men with hypogonadotrophic hypogonadism of hypothalamic origin, such as those with Kallmann's syndrome;[8,9] therapy for 1 to 2 years may be necessary to achieve adequate sperm production in some patients who have not previously received gonadotrophins or gonadorelin.[8]

In idiopathic oligospermia, results of drug therapy have been disappointing. Studies of gonadorelin have produced contradictory results and gonadotrophins have not been effective.[8] The antioestrogens, clomifene and tamoxifen, have been used in subfertile men,[9] but there is limited convincing evidence of benefit.[4,8] Corticosteroids have been used in men with autoantibodies to spermatozoa, but efficacy is unproven and corticosteroids are generally not recommended[4,8,9] although they might be considered in men with autoantibodies who have failed assisted reproduction techniques.[9] However, corticosteroids may have a beneficial effect on infertility associated with auto-immune orchitis.[9] Various other drugs have been used on an empirical basis for idiopathic male infertility but evidence for their efficacy is either limited or lacking.[8,9]

When other methods fail, assisted reproduction may be considered. Techniques for male infertility include intra-uterine insemination and intracytoplasmic sperm injection.[4,8-10]

1. ACOG Committee on Practice Bulletins—Gynecology. Management of infertility caused by ovulatory dysfunction. *Obstet Gynecol* 2002; **99:** 347–58.
2. Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in women. *Fertil Steril* 2006; **86** (issue 5 suppl 1): S187–S193.
3. Anonymous. Managing anovulatory infertility. *Drug Ther Bull* 2004; **42:** 28–32.
4. National Collaborating Centre for Women's and Children's Health/NICE. Fertility: assessment and treatment for people with fertility problems. February 2004. Available at: http://www.nice.org.uk/nicemedia/pdf/CG011fullguideline.pdf (accessed 28/07/08)
5. Holzer H, *et al.* A new era in ovulation induction. *Fertil Steril* 2006; **85:** 277–84.
6. Huirne JAF, *et al.* Contemporary pharmacological manipulation in assisted reproduction. *Drugs* 2004; **64:** 297–322.
7. Griesinger G, *et al.* Gonadotropin-releasing hormone antagonists for assisted reproductive techniques: are there clinical differences between agents? *Drugs* 2004; **64:** 563–75.
8. Dohle GR, *et al.* European Association of Urology guidelines on male infertility: update March 2007. Available at: http://www.uroweb.org/fileadmin/user_upload/Guidelines/Male%20Infertility.pdf (accessed 16/06/08)
9. Haidl G. Management strategies for male factor infertility. *Drugs* 2002; **62:** 1741–53.
10. Jarow JP, *et al.* Best practice policies for male infertility. *J Urol (Baltimore)* 2002; **167:** 2138–44.

Polycystic ovary syndrome

The polycystic ovary syndrome comprises enlargement of the ovaries with multiple follicular cysts and a thickened, whitish, capsule; there is persistent elevation of serum luteinising hormone concentrations, with a tendency to increased androgen concentrations. Women typically present with erratic menstruation, hirsutism, and obesity, although not all these features may be present; fertility is often impaired. Associated metabolic changes include hyperinsulinaemia with insulin resistance, and increased risk of developing hyperlipidaemia, hypertension, and ischaemic heart disease. The risk of endometrial cancer is also increased.

Management is essentially symptomatic. Patients should be encouraged to modify their lifestyle, to correct lipid abnormalities, and to lose weight if obese;[1,2] weight loss alone may be sufficient to improve menstrual regularity, hirsutism, and fertility. Symptoms of hyperandrogenism can be treated with an anti-androgen, such as cyproterone acetate or spironolactone, with an oestrogen or a combined contraceptive pill.[1-5] Flutamide and finasteride have also been used in these patients (see also the discussion of the management of hirsutism, p.2089).[5] In women who do not desire pregnancy, an oral contraceptive is also the recommended treatment for amenorrhoea or oligomenorrhoea.[2,5-7] Alternatively a progestogen that lacks androgenic properties may be given cyclically, in order to induce withdrawal bleeding (anovular women who do not receive hormonal treatment may be at increased risk of endometrial cancer).[3,6,7] Metformin may also improve metabolic abnormalities and menstrual regularity (see also below), and endocrinologists in the USA have suggested that it may be considered particularly for women who are overweight or obese.[1] However, other practitioners have argued that weight reduction is more effective and should be the initial management for obese women with polycystic ovary syndrome.[2]

In patients who wish to conceive, clomifene citrate is used to induce ovulation. In patients who do not respond, gonadotrophins or laparoscopic ovarian diathermy may be tried. The effects of metformin on ovulation induction are also under investigation (see below).[2,3,6,7] Patients must be monitored carefully during any therapy to induce ovulation, as women with polycystic ovaries are more prone to multiple follicle development and ovarian hyperstimulation. For further details on ovulation induction and assisted reproduction, see Infertility, above.

Insulin resistance is a feature of polycystic ovary syndrome, particularly in obese women. Small non-randomised studies of metformin have reported improvements in insulin metabolism, a reduction in circulating androgen concentrations, small reductions in body-mass index or waist/hip ratio, and improvements in menstrual cycles.[8] Previous controlled studies have found that metformin alone improved ovulation rates and menstrual cycles, and that rates could be improved further when given with clomifene citrate.[8,9] However, more recently, 2 large, placebo-controlled studies have found that metformin, either alone or with clomifene, did not improve the rate of ovulation, pregnancy, or live births in women with polycystic ovary syndrome.[2] Metformin may also improve responses to ovulation induction using follicle-stimulating hormone.[8] Long-term effects of metformin in polycystic ovary syndrome have not been studied, however, and any reduction in cardiovascular risks is yet to be established.[10] There has also been some interest in the use of thiazolidinediones, such as rosiglitazone, but these drugs can increase body-mass, which is undesirable in women who are already overweight.[5,8] Their use is considered investigational.[1]

Bromocriptine[4] may be useful in women with polycystic ovary syndrome and associated hyperprolactinaemia (see above).

1. AACE Polycystic Ovary Syndrome Writing Committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. *Endocr Pract* 2005; **11:** 126–34.
2. Norman RJ, *et al.* Polycystic ovary syndrome. *Lancet* 2007; **370:** 685–97.
3. Anonymous. Tackling polycystic ovary syndrome. *Drug Ther Bull* 2001; **39:** 1–5.
4. Hyperandrogenic Disorders Task Force. American Association of Clinical Endocrinologists medical guidelines for the clinical practice for the diagnosis and treatment of hyperandrogenic dis-

orders. *Endocr Pract* 2001; **7:** 121–34. Also available at: http://www.aace.com/pub/pdf/guidelines/hyperandrogenism2001.pdf (accessed 05/07/06)
5. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med* 2005; **352:** 1223–36.
6. ACOG Committee on Practice Bulletins—Gynecology. Polycystic ovary syndrome. *Obstet Gynecol* 2002; **100:** 1389–1402.
7. Guzick DS. Polycystic ovary syndrome. *Obstet Gynecol* 2004; **103:** 181–93. Correction. *ibid.*; 799.
8. Harborne L, *et al.* Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. *Lancet* 2003; **361:** 1894–1901.
9. Lord JM, *et al.* Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 15/09/05).
10. Royal College of Obstetricians and Gynaecologists. Long-term consequences of polycystic ovary syndrome (Guideline no. 33 issued December 2007). Available at: http://www.rcog.org.uk/resources/Public/pdf/green_top33_pcos_a.pdf (accessed 31/03/08)

Precocious puberty

Precocious puberty is commonly understood to mean the development of secondary sexual characteristics before the age of 8 years in girls or 9 years in boys; it is four to five times more common in girls. However, the age limit used to define precocious puberty in girls has been questioned.[1] Recent data from the United States suggests that puberty is occurring earlier in girls, at age 7 years for white girls, and 6 years for African-American girls. Precocious puberty is either central, due to premature activation of the hypothalamic-pituitary-gonadal axis, or peripheral, due to secretion of extrapituitary gonadotrophins or gonadal steroids independent of gonadorelin secretion from the hypothalamus or pituitary gonadotrophins. In many cases the cause is not apparent, and they are classified as idiopathic. A small proportion of cases are due to tumours. Central precocious puberty may be caused by CNS lesions secondary to diseases such as encephalitis, meningitis, or granuloma, or due to head trauma. Peripheral precocious puberty can be associated with congenital or familial syndromes such as McCune-Albright syndrome or familial testotoxicosis (familial male precocious puberty). Congenital adrenal hyperplasia (see p.1502) can also produce premature sexual development in boys and virilisation in girls.

Apart from early sexual maturation and the associated emotional distress, the chief clinical consequence of precocious puberty is short stature as an adult, due to premature closure of the epiphyses under the influence of sex steroids.[2,3] Age, emotional impact and final height potential should be considered in deciding when to begin and end treatment.[2]

Gonadorelin analogues are the treatment of choice in central precocious puberty.[2,3] The use of continuous rather than pulsatile gonadorelin can paradoxically suppress gonadotrophin secretion by desensitisation and down regulation of pituitary receptors. Cyproterone acetate has been given at the beginning of treatment to prevent the initial stimulatory effect of the gonadorelin analogue.[2] Although originally given daily, by subcutaneous injection or nasal insufflation, intramuscular and subcutaneous depot preparations of gonadorelin analogues are more convenient, and are now more widely used.[2,3] Treatment suppresses sexual development and skeletal maturation, and most studies have reported an improvement in final height.[3,4] However, the treatment of girls with borderline early puberty (between 6 and 8 years of age) has been questioned, as studies suggest that most will reach adult height within the normal range without treatment.[1] Such girls with idiopathic slowly progressing puberty, and no evidence of advanced bone age, may not require gonadorelin therapy, but should be monitored for an onset of rapid pubertal development.[1,5] Children with concomitant growth hormone deficiency (for example after cranial irradiation) may need additional therapy with somatropin or its analogues for maximum benefit.[6] Somatropin has also been used in children who do not have growth hormone deficiency but who have a poor response to gonadorelin analogue therapy; evidence for a beneficial effect is limited.[7]

In the peripheral forms of precocious puberty the gonadorelin analogues are ineffective. Any underlying condition such as a gonadal or adrenal neoplasm should be sought and treated appropriately. Otherwise, therapy is aimed at suppressing premature sexual maturation, and drugs such as cyproterone and medroxyprogesterone have been used.[8] In girls with precocious puberty associated with the McCune-Albright syndrome, the aromatase inhibitor testolactone has been used with some success to block oestrogen biosynthesis,[9,10] ketoconazole has been used in 2 cases,[11] and tamoxifen has been reported to be beneficial.[12] Although ineffective when given alone, testolactone was reported to be of benefit when used with the anti-androgen, spironolactone, in boys with testotoxicosis;[13] a reduction in the rate of bone maturation was reported. Response diminished with long-term treatment, but could be restored by the addition of a gonadorelin analogue, deslorelin, to therapy.[14] This regimen has also been reported[15] to improve predicted adult height. Ketoconazole, which has anti-androgenic properties, has also been tried in boys with familial male precocious puberty; it had beneficial effects on testosterone concentrations and adult height reported in a series of 5 patients.[16]

1. Kaplowitz PB, *et al.* Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. *Pediatrics* 1999; **104:** 936–41.
2. Merke DP, Cutler GB. Evaluation and management of precocious puberty. *Arch Dis Child* 1996; **75:** 269–71.
3. Partsch C-J, *et al.* Management and outcome of central precocious puberty. *Clin Endocrinol (Oxf)* 2002; **56:** 129–48.
4. Klein KO, *et al.* Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *J Clin Endocrinol Metab* 2001; **86:** 4711–16.
5. Léger J, *et al.* Do all girls with apparent idiopathic precocious puberty require gonadotropin-releasing hormone agonist treatment? *J Pediatr* 2000; **137:** 819–25.
6. Adan L, *et al.* Adult height in 24 patients treated for growth hormone deficiency and early puberty. *J Clin Endocrinol Metab* 1997; **82:** 229–33.
7. Walvoord EC, Pescovitz OH. Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: theoretic and practical considerations. *Pediatrics* 1999; **104** (suppl): 1010–14.
8. Stanhope R, Traggiai C. Precocious puberty (complete, partial). *Endocr Dev* 2004; **7:** 57–65.
9. Feuillan PP, *et al.* Long term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. *J Clin Endocrinol Metab* 1993; **77:** 647–51.
10. Albers N, *et al.* McCune-Albright syndrome - the German experience. *J Pediatr Endocrinol Metab* 2002; **15** (suppl): 897–901.
11. Syed FA, Chalew SA. Ketoconazole treatment of gonadotropin independent precocious puberty in girls with McCune-Albright syndrome: a preliminary report. *J Pediatr Endocrinol Metab* 1999; **12:** 81–3.
12. Eugster EA, *et al.* Tamoxifen treatment for precocious puberty in McCune-Albright syndrome: a multicenter trial. *J Pediatr* 2003; **143:** 60–6.
13. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; **320:** 496–502.
14. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
15. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.
16. Soriano-Guillén L, *et al.* Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. *J Clin Endocrinol Metab* 2005; **90:** 147–51.

Premenstrual syndrome

Gonadorelin analogues have been used to treat patients with severe symptoms attributable to the premenstrual syndrome (p.2099), with 'add-back' therapy with oestrogen plus progestogen to prevent the symptoms of oestrogen deficiency.

Turner's syndrome

Turner's syndrome is a congenital disorder associated with the absence of an X or Y chromosome, resulting in an individual with only a single X chromosome who is female in phenotype but in whom the ovaries do not develop. In addition to this gonadal dysgenesis, which results in infertility and primary amenorrhoea, various physical abnormalities may be present including short stature, a short webbed neck and characteristic facial appearance, shield-like chest, multiple naevi, and certain renal and cardiovascular abnormalities. Hypothyroidism and glucose intolerance may occur.

As with other forms of ovarian failure, HRT with oestrogen and intermittent progestogen is indicated in women with Turner's syndrome, in order to produce sexual maturation and the development of secondary sexual characteristics as well as to avoid complications such as osteoporosis. Clinical opinion has generally been that therapy should begin with low doses of oestrogen in girls of prepubertal age, gradually increasing the dose to promote slow development of secondary sexual characteristics and eventual breakthrough bleeding, at which point a cyclic progestogen should be added to oestrogen maintenance to minimise the risk of endometrial hyperplasia and cancer. In general, therapy is started around 14 to 15 years of age, but may be started as early as 12 years of age in girls who have reached a satisfactory height, especially those who have been treated with growth hormone.[1-3] There is no consensus on which oestrogen is preferred for these patients; conjugated oestrogens, ethinylestradiol, and estradiol have all been used. An oral contraceptive may be used for maintenance therapy.[3]

A minority of patients with Turner's syndrome have some residual ovarian function, and there are a few reports of pregnancy in such patients. In women without ovaries it may be possible to maintain pregnancy by appropriate endocrine replacement after implantation of a fertilised donor egg.[1]

Short stature is the most common clinical manifestation of Turner's syndrome. Growth hormone therapy has been widely used and may be considered from as early as 2 years of age,[2] but there is considerable debate about the extent of the benefit in terms of final height. Results from 622 girls enrolled in the National Cooperative Growth Study[4] suggested a mean height gain of 6.4 ± 4.9 cm, and another cohort database[5] of 485 girls found that when treatment was started before puberty a mean increase in final height of 5 cm or more would be expected. A systematic review[6] of 4 controlled studies found that growth hormone increased short-term growth, but that there was limited controlled data on final height. It has been suggested[1] that a final height of 150 cm is an achievable goal for most patients. Growth hormone therapy during childhood and adolescence may also be important in maximising bone mass and reducing the risk of osteoporosis.[7] Although it is generally recommended that oestrogen replacement be delayed where growth promotion is a priority,[1,2] optimal oestrogen replacement therapy may also be important in maximising final height. In a comparison[8] of the introduction of conjugated oestrogen therapy at 12 or 15 years of age, the combination of growth hormone and oestrogen initially stimulated growth velocity and bone maturation more than growth hormone alone, but subsequently declined after about 2 years. Patients who received growth hormone for a longer period before starting oestrogen therapy attained greater adult height, a finding also noted in another study;[9] it was suggested that early use of growth hormone could allow oestrogen therapy to be begun at a more appropriate, younger age without compromising final height. However, the use of low-dose oestrogen from an even earlier age (as young as 8 years) to stimulate linear growth does not add to the effect of growth hormone therapy and may even reduce final height.[10] Combination of growth hormone with a non-aromatisable anabolic steroid such as oxandrolone is recommended as an option in girls aged 8 to 12 years if therapy is begun late,[1] or if response to growth hormone is inadequate.[2]

Adult women with Turner's syndrome require multidisciplinary management including cardiovascular monitoring, psychological support, and a programme of prevention for diabetes, osteoporosis, and hypertension.[1,2]

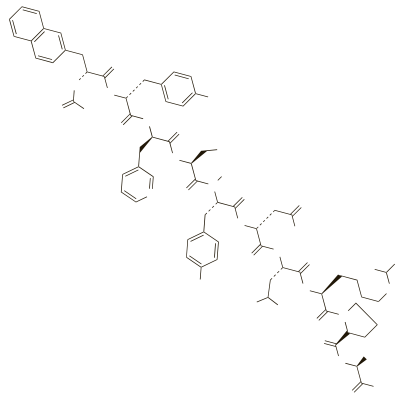
1. Saenger P, *et al.* Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab* 2001; **86:** 3061–9.
2. Frías JL, *et al.* Health supervision for children with Turner syndrome. *Pediatrics* 2003; **111:** 692–702.
3. Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004; **351:** 1227–38.
4. Plotnick L, *et al.* Growth hormone treatment of girls with Turner syndrome: the National Cooperative Growth Study experience. *Pediatrics* 1998; **102:** 479–81.
5. Betts PR, *et al.* A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Arch Dis Child* 1999; **80:** 221–5.
6. Cave CB, *et al.* Recombinant growth hormone in children and adolescents with Turner syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 15/09/05).
7. Rubin K. Turner syndrome and osteoporosis: mechanisms and prognosis. *Pediatrics* 1998; **102** (suppl): 481–5.
8. Chernausek SD, *et al.* Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. *J Clin Endocrinol Metab* 2000; **85:** 2439–45.
9. Reiter EO, *et al.* Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 2001; **86:** 1936–41.
10. Quigley CA, *et al.* Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. *J Clin Endocrinol Metab* 2002; **87:** 2033–41.

Abarelix *(USAN, rINN)*

Abarélix; Abarelixum; PPI-149; R-3827. *N*-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-*N*-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-*N*^{6}-isopropyl-L-lysyl-L-prolyl-D-alaninamide.

Абареликс

$C_{72}H_{95}ClN_{14}O_{14}$ = 1416.1.
CAS — 183552-38-7.
ATC — L02BX01.
ATC Vet — QL02BX01.



Adverse Effects and Precautions

Immediate hypersensitivity reactions, including urticaria, pruritus, hypotension, and syncope, can occur with abarelix, and the cumulative risk of such a reaction increases with repeated doses. Patients should be monitored for at least 30 minutes after each injection. Hot flushes, sleep disturbance, breast enlargement and tenderness may result from testosterone reduction. Prolongation of the QT interval has occurred in patients receiving abarelix.

Elevations in transaminase concentrations have occurred, and liver function should be monitored before starting treatment, and periodically during treatment. The effectiveness of abarelix in the management of prostate cancer decreases with duration of therapy, and may be further reduced in patients weighing more than about 100 kg (225 pounds). The serum concentration of testosterone should be measured on day 29 of therapy and then every 8 weeks, to monitor for treatment failure.