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GUIDELINES

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Society for endocrinology guideline for understanding, diagnosing and treating female hypogonadism

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Abstract

Female hypogonadism (FH) is a relatively common endocrine disorder in women of premenopausal age, but there are significant uncertainties and wide variation in its management. Most current guidelines are monospecialty and only address premature ovarian insufficiency (POI); some allude to management in very brief and general terms, and most rely upon the extrapolation of evidence from the studies relating to physiological estrogen deficiency in postmenopausal women. The Society for Endocrinology commissioned new guidance to provide all care providers with a multidisciplinary perspective on managing patients with all forms of FH. It has been compiled using expertise from Endocrinology, Primary Care, Gynaecology and Reproductive Health practices, with contributions from expert patients and a patient support group, to help clinicians best manage FH resulting from both POI and hypothalamo-pituitary disorders, whether organic or functional.

KEYWORDS
estrogen, female, guideline, hypogonadism, menopause, ovarian insufficiency

1 | INTRODUCTION

Female hypogonadism (FH) results in amenorrhoea with deficient ovarian folliculogenesis, impaired sex hormone secretion, anovulation and, frequently, sexual or vasomotor symptoms during the age range from normal puberty to normal menopause. It is usually characterised biochemically by a persistently low circulating serum 17β-estradiol (estradiol) concentration.

FH can be either due to a lack of hormone-producing follicles within the ovary, characterised by raised concentrations of the gonadotropins, follicle-stimulating hormone (FSH) and luteinising hormone (LH), or to inadequate gonadotropin stimulation, wherein FSH and LH concentrations are low although they may still lie within the laboratory-defined normal range. The former is termed premature ovarian insufficiency (POI) and the latter hypogonadotrophic- or central hypogonadism (CH). Clinically, FH has consequences for general health and well-being on women beyond issues of external sexual characteristics, sexual function and fertility.

The diagnosis of FH becomes trickier with the presence of other potential causes of prolonged amenorrhoea, such as features of polycystic ovary syndrome (PCOS), or the use of progestogen-based hormonal contraception, for which the key FH symptom of amenorrhoea is an anticipated or even desired effect. The diagnosis of FH may be missed unless the clinician asks direct questions in relation to potential symptoms attributable to estrogen deficiency and carefully scrutinise the biochemistry and other investigations.[1] Although PCOS and CH can coexist, a low estradiol concentration and a sonographically thin endometrium would tend to indicate CH, irrespective of the ovarian morphology or the androgen profile.

Suggested biochemical cut-offs for FH have varied between investigators, but have largely been side-stepped by existing monospecialty guidance.[2] Laboratory reference ranges are unhelpful in this context, as they necessarily benchmark a particular phase of the menstrual cycle for a *normally cycling* woman (in whom it is hard to envisage any useful clinical indication for measuring serum estradiol in the first place). These reference ranges thus do not usefully contribute to the diagnostic evaluation of a woman with amenorrhoea and suspected FH. For clarity and simplicity, we propose that an estradiol concentration persistently below 200 pmol/L *in the context of amenorrhoea of at least 3 months' duration* is consistent with FH; not necessarily diagnostic in itself, but requiring the diagnosis to be seriously considered, even when there are other possible explanations for amenorrhoea and particularly where there are other supportive symptoms and signs.

The association with amenorrhoea is critical, since estradiol concentrations down to 100 pmol/L may also be observed in the premenstrual phase of normally cycling women.[3] In addition to the simplicity of a round number in SI units, our proposed threshold of 200 pmol/L is underpinned by the range of serum estradiol concentrations observed in women with hypothalamic and lactational forms of amenorrhoea, as described in Section 4.4, However, as described in Section 4.2, because acquired POI may have a stuttering onset, normal hormone levels at any given point do not necessarily refute the diagnosis when the diagnosis is suspected.

The accepted timeframe for female reproductive life extends from menarche (around 13 years of age) to the menopause (45–55 years; median 51 years).[4,5] Women who lose ovarian function between 40 and 45 years are defined as having early menopause rather than POI, but also fall within the scope of this guidance, because an earlier age of menopause is associated with an increased risk of cardiovascular disease (CVD),[5–7] osteoporosis and fracture.[7]

Although post-menopausal women, gonadectomised transgender women and, indeed, pre-pubertal girls share similar characteristics to reproductive age women with hypogonadism, they do not fall within the conventional definition of FH or the direct scope of this guidance. Therefore, this guidance does not address regimens for the induction of puberty in girls, the feminisation of transgender women, nor the hormone treatment of women who underwent menopause around or after the median age of menopause (MAM)—although there are some useful transferable lessons and practices.

FH can manifest at any point in normal reproductive life from puberty onwards, although certain clinical features or diagnoses identified during normal prepuberty may already signpost the expectation of FH, such as Turner syndrome (TS), combined pituitary hormone deficiency (CPHD), septo-optic dysplasia (SOD), or CHARGE syndrome (coloboma, heart defect, choanal atresia, growth retardation, genital and ear anomalies). Crucially, although women who develop FH closer to MAM are numerically far more common, those who develop it earlier in life will necessarily spend a far greater proportion of their lives under medical supervision for hormone treatment, potentially for up to 40 years.

In the UK healthcare environment, women with FH are also managed by Gynaecologists and General Practitioners, as well as by Endocrinologists, although cases of FH relating to hypopituitarism, or having other significant Internal Medicine issues will usually benefit from having Endocrinologist-led care.

2 | METHODS

The Society for Endocrinology (SfE) is a professional and scientific organisation dedicated to the advancement of knowledge and the promotion of good practice in the field of Endocrinology. Although based in the United Kingdom, it is not a narrowly national body and, indeed, many committee members and officers practice in the Republic of Ireland. The commissioning and development broadly followed the model for SfE's guidelines on male hypogonadism, which shared the same co-chairs and one other working group member.[8]

The SfE's Clinical Committee commissioned this Guideline and appointed CNJ and RQ as co-chairs. The Clinical Committee and co-chairs nominated a working-group to represent multiple disciplines relevant to the guideline. Patient members and a representative of a patient support group (Turner Syndrome Support Society UK) were also nominated to attend all meetings and approve decisions alongside the other members of the working group.

The scope was confined to the management of adult women who experienced or developed primary or secondary ovarian insufficiency before the usual age at menopause, Although we predominantly focused on the needs of younger women below 40 years of age, this guidance is also applicable to the approximately 5% of women with 'early menopause' (or other cause of FH) between the ages of 40 and 45 years.[9,10] We did not address the management of pubertal induction in women and girls with FH, for which we signpost the reader to several recent publications including Federici et al.,[11] Howard and Quinton,[12] and Nordenström et al.[13]

Meetings (face-to-face and remote) were held between November 2021 and October 2023 to assign specific areas of the guideline scope for individual members of the working group to perform narrative reviews of the literature in that area and, as progress was made, for members to provide reports on their assigned topic to the collective group. On rare occasions where complete consensus could not be reached on specific points, the co-chairs were authorised to make the final determination of content. An advance draft of this guideline was revised following internal peer review by the SfE Clinical Committee, before submission for publication.

3 | THE BIOLOGICAL EFFECTS OF THE FEMALE SEX HORMONES

Estradiol is the major hormone of deficiency in hypogonadism in women, but it is also essential to consider the importance of progesterone. The role of androgens, notably testosterone but also weak adrenal androgens, is more controversial although they have contributory actions in normal female physiology. Adrenal androgen secretion is impaired in women with hypopituitarism and ACTH deficiency, but not with other forms of FH, although ovarian androgen secretion is impaired in all forms. This section very briefly reviews the main physiological effects of the sex steroids of relevance to replacement therapy, though it is important to consider how closely pharmacological replacement mimics physiology.

Estradiol is essential for the key secondary sex characteristics, emerging normally at puberty. These effects develop over several years with thelarche being the initial sign, initiated with still low levels of circulating estradiol.[14] This highlights the need for an appropriate pace of incremental estrogen administration to mimic normal puberty, with the avoidance of early progesterone exposure which can affect full development of the breast by limiting the branching morphogenesis necessary for complete development of the ductal tree,[15] and may also limit uterine development.[11] Estradiol is also essential for uterine growth and maturation, and ongoing health of the urogenital tract. The vaginal epithelium requires estrogen for proliferation and keratin production and there is also evidence of a role in immune regulation.[16] This is increasingly topical with increasing interest in the vaginal microbiome and its role in sexual and reproductive health, including in states of estrogen deficiency.[17]

In addition to its role in uterine growth, estradiol is essential for cyclic endometrial repair and proliferation after menstruation. Estrogen exposure is also necessary for the expression of endometrial progesterone receptors, underlying the necessary changes to a secretory pattern which are required for embryo implantation and the establishment of pregnancy.[18]

Centrally acting estrogen negatively regulates hypothalamic kisspeptin (Kp) and gonadotrophin-releasing hormone (GnRH), which is the principal regulator of reproduction, controlling pituitary gonadotrophin secretion and, thereby, ovarian function. Distinct hypothalamic kisspeptin neuronal populations mediate estrogenic positive feedback to generate the mid-cycle GnRH/LH surge necessary for ovulation. Estradiol also acts on the gonadotrophs of the anterior pituitary to regulate FSH and LH secretion, physiologically in concert with other ovarian hormones, notably the inhibins, in the regulation of FSH secretion.[19] This locus of action is also very important in generating the mid cycle LH surge. It is now recognised that kisspeptin neurons also project from the infundibular nucleus to the medial preoptic nucleus, where they innovate the warm sensing neurons (signalling primarily through neurokinin B-mediated synaptic activity), whose excess activity in states of hypergonadotrophic estrogen deficiency results in the characteristic vasomotor symptoms of the menopause,[20] which are notably absent when the cause is hypogonadotrophic or with very early onset POI.

Estrogen receptors are also very widely expressed across the body, with notable effects on regulating bone, brain, cardiovascular and metabolic function. Within bone, estradiol controls both osteoblast and osteoclast number and function, through which it regulates both cortical and trabecular bone turnover.[21] Effects on other physiological systems have been less comprehensively studied and controversy remains, but there is increasing evidence that estrogen is required for continuing cardio-metabolic and, potentially, neurocognitive health.[22–24] Evidence of relevance to hypogonadism in young women is, however, largely indirect. Surgical oophorectomy in premenopausal women is associated with several adverse effects across these physiological systems,[25] including an increased risk of cardiovascular disease and—at least in the short-medium term—neurocognitive impairment.[26] However, some of these effects might relate to the sudden withdrawal of ovarian hormones, and may thus not be so applicable to the waxing and waning of these same hormones experienced during the onset of most spontaneous hypoestrogenic states, or to the complete absence of puberty, where the body has never been exposed to normal adult levels of estradiol and vasomotor symptoms are unusual.

Estrogen regulates cerebral blood flow, flow-mediated blood vessel dilatation and regulates hepatic lipid metabolism.[14,27–29] It increases cleavage of small dense low-density lipoprotein (LDL) particles and increases endothelial nitric oxide synthase, thus

increasing production of nitric oxide, with additional effects on other pathways such as renin-angiotensin (especially with EE) and salt sensitivity that regulate blood pressure.[30] Other aspects of endothelial function may also be enhanced. Through effects on mitochondrial bioenergetics, estrogen is an important regulator of insulin sensitivity with actions on adipose tissue, liver, muscle and pancreatic beta cells.[31]

The key role of progesterone is in preparing the endometrium for implantation. It limits the proliferative action of estrogen and thus counteracts the pathological effects of unopposed estrogen exposure. Progesterone also acts on bone, albeit with limited effect compared to estradiol.[32] It may also have neuroprotective effects, but the evidence on whether this is of clinical relevance is difficult to disentangle from controversies over the effects of estrogen replacement and the varied pharmacology of synthetic progestogens.[33–35]

The ovary is a significant source of testosterone and other androgens, with reduced production in women with both POI,[36] and hypogonadotrophic (or central) hypogonadism (CH). The clinical implications of this are unclear, although it may impact on sexual health,[37] and it is important to recognise the substantial interconversion of sex steroids that occurs in peripheral tissues and organs. Thus half of circulating testosterone in women derives from peripheral conversion of androstenedione, and testosterone itself is a direct precursor to estradiol.

4 | CAUSES OF FEMALE HYPOGONADISM

4.1 | Why is it important to establish the nature of FH?

Serum estradiol concentrations that are persistently below 200 pmol/L in the presence of amenorrhoea and relevant clinical features are consistent with FH. Progesterone challenge tests do not adequately distinguish between FH and non-FH forms of amenorrhoea and add no additional diagnostic information beyond that provided by basal hormone levels or sonographic measurement of endometrial thickness. However, the additional measurement of serum FSH and LH concentrations is necessary to distinguish women with CH from those with POI, which is a mandatory clinical requirement because the outcome of these analyses determine:

- The nature of confirmatory or second-line investigations, such as pituitary biochemical profiling and imaging in CH, versus those relevant to the aetiology of POI, such as determination of karyotype or copy number variation.
- The range of potential sub-diagnoses, which can in turn signpost specific disease management strategies beyond sex hormone therapy, for example, screening, identification of risk-mitigation for type 2 diabetes (T2DM), cardiovascular disease, aortopathy, liver abnormalities, autoimmune disease or hearing impairment in women with previously unsuspected Turner syndrome, versus screening for hyperprolactinaemia, iron overload, wider pituitary dysfunction, relative energy deficit, or a parasellar mass in women with CH.
- The available first-line options for inducing/restoring fertility, which differ fundamentally: gonadotrophin therapy to induce ovulation (or controlled ovarian hyperstimulation for in vitro fertilisation—IVF) in CH versus egg or embryo donation (or nonmedical approaches such as adoption) in POI, as strategies for achieving parenthood.
- The nature of FH through further contextual clinical ascertainment. For instance, the primary diagnosis is invariably secure when basal biochemistry indicates POI, for which first line therapy is hormone replacement therapy (HRT) to at least MAM, whereas further contextual clinical ascertainment is required to properly distinguish between organic and functional or iatrogenic forms of CH.

Crucial to identifying the aetiology of CH is ruling out potential causes and confounders, which demands contextual clinical history, targeted physical examination, medication review and, potentially, further biochemical or radiological assessment. A schematic outlining the general subdivisions of female hypogonadism is presented in Figure 1, but does not cover the full extent of granularity. For instance, functional CH (more commonly known as hypothalamic amenorrhoea—HA) may be induced by relative energy deficit (usually in the context of psychosocial or physical stress), long-term use of opiates, or on occasion, depot intramuscular progestogen contraception (Depo-Provera®) (described further in Section 4.4).

4.2 | Premature ovarian insufficiency (POI)

4.2.1 | Terminology and definitions

The term premature ovarian insufficiency is now most widely used although 'primary' ovarian insufficiency is also current and conveniently the same abbreviation (POI) refers to both. POI is characterised by menstrual disturbance (usually oligo-amenorrhoea) in the setting of abnormally raised serum FSH and low estradiol concentrations (usually below 200 pmol/L).

Having established a primary diagnosis of POI, the further diagnostic workup should include: a personal and family medical history; karyotype; *FMR1* gene screening; thyroid stimulating hormone (TSH); Thyroid Peroxidase antibody concentration and, potentially, NHS Genomics R402 panel.

Excluding postsurgical cases, POI was traditionally considered to affect around 1% of women before age 40 years (and around 0.1% before age 30). However, likely as a result of improved case ascertainment and (potentially) greater cancer survivorship into adult life, the prevalence of POI in more recent studies is notably higher (2%–3.7%).[38,39]

POI can be of either prepubertal or postpubertal onset; and clinicians should be aware of which form (and, if acquired, at approximately what age) in respect of patient management. In the

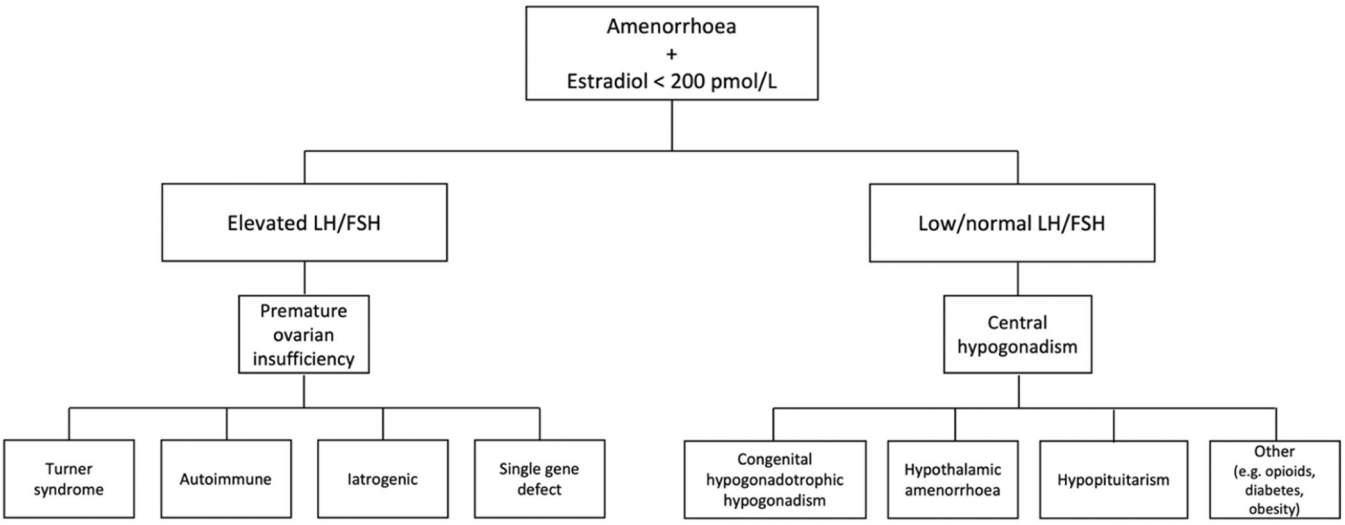

FIGURE 1 Hypogonadism should be considered in females with prolonged amenorrhoea and estradiol levels <200 pmol/L. Measurements of follicle stimulating hormone (FSH) and luteinising hormone (LH) delineate primary/ovarian versus central causes, the most common being outlined above.

category of POI of prepubertal onset, we include all forms of gonadal dysgenesis, whether 46,XX, 46,XY or the various karyotypes associated with Turner syndrome (albeit not all women with Turner have gonadal dysgenesis; some acquire POI postpuberty, and a few even maintain ovarian function up to normal age of menopause). Unless a particular disorder was already identified in childhood due to the presence of other developmental anomalies, POI related to gonadal dysgenesis should always present with primary amenorrhoea and absent puberty in adolescence. Although congenital disease tends to result in POI of prepubertal onset with primary amenorrhoea and absent puberty, this is not invariably the case. Examples of genetic defects being able to cause either primary or secondary amenorrhoea include type 1 galactosaemia (*GALK1* gene) due to accumulation of abnormal metabolites, premutation expansions of the *FMR1* gene, and the aforesaid minority of women with mosaic Turner syndrome.

The presentation of nonsurgical acquired POI is varied, with classical vasomotor symptoms sometimes absent, and more subtle features, such as mood change, fatigue, cognitive impairment, joint stiffness and pain and sexual dysfunction, being evident but often only on direct questioning. It is important to take both a personal and family history. Crucially, acquired POI may have a stuttering onset, so that ovulation may still occur and hormone levels may periodically return to normal, especially in the early years after diagnosis. Therefore, normal hormone levels on a repeat sample do not override the original suspicion of POI. Moreover, chemotherapy-induced POI may also recover, albeit with a reduced ovarian reserve and thus a significant risk of early menopause thereafter.[40] In a study of Australian women with acquired POI, the diagnosis took longer than 2 years in 23% of women, and with at least two clinicians having been consulted on average.[41]

4.2.2 | Turner syndrome and other forms of gonadal dysgenesis

Turner Syndrome is the commonest sex chromosome disorder in females and may result from complete or partial loss of the X chromosome, or structural abnormalities of the X chromosome. It is typically associated with POI, and a broad range of other clinical features including short stature, cardiovascular abnormalities, autoimmune conditions, and metabolic features.[42] A mosaic karyotype is usually associated with less severe phenotype and there are some karyotype/phenotype correlations. While up to one-third of girls with TS may develop spontaneous thelarche, spontaneous menarche occurs in 5%–20%, and less than 10% develop regular periods; higher when mosaicism is present and lower with 45,X.

Other less common disorders of sexual differentiation include disorders of androgen synthesis or gonadal development.[43] 46,XY gonadal dysgenesis (Swyer syndrome) carries a high risk of gonadoblastoma, so pelvic magnetic resonance imaging (MRI) is mandatory at diagnosis to identify streak gonads for removal.[44] Other rare causes include disorders of Mullerian development or androgen action.[43]

4.2.3 | Single gene defects causing POI

Where the karyotype is normal and there are no features of autoimmunity, the causes of POI remain largely unknown, but could potentially include polygenic disease or form part of a premature ageing syndrome.[45–48] Nevertheless, a growing number of individual genes have been linked to POI, albeit with varying strength of evidence[49–51]; the best established is the FMR1 premutation found in around 3% of sporadic and 15% of familial cases of POI,[52] albeit

with a high rate of under-diagnosis in the general population.[53] Affected women harbour 50–200 CCG triplet repeats within the 5′ untranslated region of the *FMR1* gene, rather than the normal <45, or over 200 in Fragile X syndrome. This 50–200 expansion range is also now recognised to carry an increased risk of tremor and ataxia syndrome. Female relatives may also carry this expansion, which may expand to the full mutation of over 200 repeats and result in Fragile X syndrome with mental disability, which is more severe in male offspring. Genetic testing for this condition is recommended in spontaneous POI under 30 years of age. Genetic mitochondrial myopathies may also cause POI.[54,55]

4.2.4 | POI following surgery or nonsurgical cancer treatment

In addition to the obvious situation of following bilateral oophorectomy, less drastic ovarian surgery is an important risk of later POI. This encompasses removal of benign cysts, including dermoids and endometriomata, especially when they are large, or surgery is repeated. There is also a growing population of young women who have survived cancer and its treatment, whose ovarian function may have been damaged or destroyed by chemotherapy, radiotherapy, or surgery. The risks from chemotherapy and radiotherapy vary by regimen, dose, and age at administration, and are comprehensively reviewed elsewhere.[40] Amenorrhoea with low estrogen production is also common during and immediately after chemotherapy, and is temporary in 70% of those diagnosed with cancer between 20 and 35 years of age. The rate of recovery also varies by age and diagnosis,[56] with restoration of menses within 2 years in 90% of women who recover ovarian function, albeit usually with a reduced ovarian reserve and thus the risk of early menopause thereafter.[57]

4.2.5 | POI presumed to arise from autoimmunity

Up to 30% of karyotypically normal cases of acquired POI may be associated with autoimmunity. However, true autoimmune oophoritis (selective theca cell destruction) is uncommon (only 4% to 5% of cases), characterised by multiple follicles on ultrasound, normal to high serum inhibin B and LH levels that are higher than FSH, unlike other forms of POI.[58,59] An autoimmune aetiology is generally presumed where another autoimmune condition is present, whether endocrine (as part of a polyglandular syndrome, with antibody-mediated oophoritis resulting in destruction of ovarian follicles), or non-endocrine; less compellingly with positive autoantibodies of any type in the absence of any defined autoimmune disease.[45]

Affected women may rarely experience brief disease remissions that allow them to ovulate and fall pregnant, particularly in the early years after onset. Nearly three out of four women with karyotypically normal POI retain ovarian follicles, but chronically raised LH levels promote premature luteinisation, which diminishes the chances for spontaneous ovulation over time.[60]

Therefore, not only can a slightly more positive perspective on fertility potential be shared with patients, but consideration of contraception should also form part of the discussion. However, in practice, the *lifetime* chance of conceiving naturally is approximately 5%,[45] compared with the 5% *annual* conception rate for a fertile woman making careful use of barrier contraception.

As to the screening bloods to request in a woman with POI lacking any other obvious autoimmune disease and whose genetic screen is negative, the following could be considered in descending order of clinical relevance: thyroid stimulating hormone (TSH), Thyroid Peroxidase antibodies, adrenal antibodies, vitamin B_{12}, gastric parietal cell and coeliac antibody screen. However, no firm recommendations can be made based on current evidence.

There is no useful anti-ovarian antibody test—even though many laboratories will offer one—as it is not specific enough to indicate any clinical correlations. Anti-adrenal cortex antibodies or anti-21-hydroxylase antibodies are probably more useful, as these have been shown to be associated with lymphocytic infiltration of the ovary (oophoritis), with destruction of follicles commencing from the thecal layers inwards. Biochemically, this can manifest as higher LH than FSH elevations, in contrast to the normal situation in POI and menopause, and in some with relative preservation of AMH concentrations. Those who test positive for these antibodies should have an endocrine review to investigate their adrenal function, as they may be at risk of adrenal insufficiency (autoimmune Addison's disease). Although it has been suggested that all women with unexplained POI should be offered adrenal cortex antibody or 21-hydroxylase antibody testing,[61] in clinical practice, the detection of those with subclinical or latent Addison's disease is rare. Conversely, POI occurs in 8%–20% of women with isolated autoimmune Addison's and 40%–60% of those when Addison's is part of autoimmune polyendocrine syndrome type 1 (APS-1/APECED).[62]

4.2.6 | Miscellaneous and environmental factors

These include mumps oophoritis and, potentially, various endocrine disruptors, heavy metals, solvents, pesticides and industrial chemicals, although direct causative evidence is slim or equivocal. Cigarette smoking, excessive alcohol consumption and hysterectomy are associated with an earlier onset of menopause, but usually only by around a year or so individually,[63,64] and are thus unlikely to tip the balance towards developing POI in any given woman.

4.3 | Hypothalamic and pituitary disorders—central hypogonadism (CH)

4.3.1 | Terminology and definitions

The hypothalamic–pituitary–gonadal (HPG) axis is central for human reproduction and comprises the neuroendocrine networks that integrate wide-ranging internal homeostatic and external environmental

inputs to coordinate reproductive competence. For co-ordinated pulsatile secretion to occur, GnRH neurons must first migrate during embryonic development from the olfactory placode to the mediobasal hypothalamus along fascicles of the accessory olfactory nerves. Upon arrival, they must form a co-ordinated neural network and also establish a regulatory relationship with higher-order hypothalamic centres (including Kp neurones) that integrate the relevant neuroendocrine signals, crucially including leptin secreted from white adipose tissue.[65]

Either genetic disruption of these developmental processes, or disruption of neurohumoral regulatory pathways during adult life may compromise effective GnRH-stimulated release of gonadotrophins from the anterior pituitary gland, constituting CH. Thus, CH is the only form of female infertility that is remediable with direct hormone replacement, whether with gonadotropins or (much less commonly, as it is less frequently indicated and there is currently no commercially available product) GnRH ovulation induction. The fertility outlook is thus much brighter than in POI.[66]

CH falls broadly into organic and functional categories, with the former characterised by irreversible CH, which can be congenital or acquired. Among the congenital forms is congenital hypogonadotrophic hypogonadism (CHH), termed Kallmann syndrome if there is associated anosmia, CHARGE syndrome if there are more profound nonreproductive defects and CPHD (combined pituitary hormone deficiency) if there is wider anterior pituitary dysfunction. Alternatively, CH can be acquired in later life due to parasellar tumours, surgery, trauma (e.g. skull fracture, pituitary stalk dissection and military blast injury), hypophysitis, radiotherapy, infection, infiltrative or metabolic disorders (e.g. iron overload) or infarction following post-partum haemorrhage (Sheehan's syndrome).[67]

4.3.2 | Congenital hypogonadotrophic hypogonadism (CHH)

Isolated CHH (with otherwise normal pituitary function) is an even rarer disorder in females (1/40,000 to 1/125,000) than in males, caused by isolated GnRH deficiency and clinically characterised by absent or incomplete puberty and infertility.[65,68] When CHH occurs with anosmia (lack of sense of smell), it is termed Kallmann syndrome. While sense of smell and reproduction may appear to be unrelated functions, the embryonic origins of GnRH neurons in the olfactory placode provide the development link.

More than 30 genes have been identified as underlying CHH, either alone or in combination.[65] Some gene mutations disrupt GnRH neuron development and migration manifesting as Kallmann syndrome; others may disrupt GnRH homeostasis, secretion or action and clinically present as cases of normosmic CHH.[65,69] NHS Genomics offers screening of a limited panel (R148) of genes.

Crucially, the Mendelian genetic architecture of CHH as presently understood does not explain why it should be 3–5 times as common in males than females. It is hypothesised that females are less likely to be referred to tertiary centres; more likely to be labelled with a functional cause such as HA, and more likely to be prescribed empirical treatment with COC without a formal diagnosis being made. However, interrogation of the Finnish national paediatric data set for hospitals suggests that the sex difference in prevalence may be genuine.[68]

CHH may occur with other associated phenotypes such as renal agenesis, hearing loss, midline defects (cleft lip/palate), dental and skeletal anomalies. It may be difficult to distinguish from other causes of pubertal delay and, consequently, many patients are diagnosed late with significant psychosocial impact.[70] These patients need psychological support and may benefit from peer-to-peer support. Although there is no 'single point of access' support group, there are some excellent online forums (e.g. https://delayed-puberty.com/).

4.3.3 | Other forms of CHH

Other forms of CHH (listed below) present with a constellation of developmental features of which hypogonadism forms only a part of the overall clinical picture. Cases are typically identified during childhood, rather than at or after normal age of menarche, because anterior pituitary hormone deficiency, obesity, skeletal, or neurodevelopmental disorders will generally command attention well before absent puberty manifests.[71]

4.3.4 | Combined pituitary hormone deficiency (CPHD), including septo-optic dysplasia (SOD)

Patients with combined pituitary hormone deficiency (CPHD) are often diagnosed early in childhood, or even neonatally, and treated for the respective pituitary hormone deficiencies, yet gonadotrophin deficiency may not become apparent until the failure of puberty to commence spontaneously. A number of genes have been identified to underlie this condition yet the majority of cases remain without an identified genetic cause.[72]

Septo-optic dysplasia (SOD) is a related developmental brain malformation that can present with pituitary hormone deficiencies, severe visual impairment, neurocognitive disability and developmental disorders on the autism spectrum, in addition to agenesis of the corpus callosum or optic nerve hypoplasia.[73]

Notably, genetic overlap has been reported between SOD, CPHD, CHH and CHARGE syndrome.[69,74] NHS Genomics offers a screening panel (R159), but the CHH panel (R148) may also be worth doing due to the overlap.

4.3.5 | CHARGE syndrome

The constellation of coloboma (ocular malformation of the lens, iris, or retina), congenital heart defects, choanal atresia (abnormal formation of the nasal cavity), retardation of growth and development, genital hypoplasia, and ear anomalies associated with deafness define CHARGE syndrome.[75] In addition to immunologic problems,

patients with CHARGE syndrome frequently exhibit CHH necessitating treatment. Approximately two-thirds of cases are explained by mutations in Chromodomain-helicase-DNA-binding protein 7 (*CHD7*), a gene also involved in CHH and Kallmann syndrome.,[69,75] offered as part of the NHS Genomics R148 panel.

4.3.6 | Prader willi syndrome

Prader Willi syndrome (PWS) is a rare genetic disorder (1/10,000–25,000), associated with severe hypothalamic dysfunction caused by lack of expression of the paternal copy of maternally imprinted genes in the chromosome region 15q11–13, with subtypes of PWS classified into deletion (70%), maternal uniparental disomy (25%–30%), imprinting centre defects (3%–5%) and rare unbalanced translocations.[76] PWS causes physical, endocrinological, mental and social disability. Puberty is usually delayed or incomplete due to CHH, but occasionally may be precocious and females are usually infertile. As well as HRT, patients typically benefit from growth hormone treatment—during childhood and adolescence at least—and multifaceted obesity-management.[77]

4.3.7 | Parasellar tumours causing central hypogonadism

These comprise craniopharyngiomas, Rathke's cleft cysts, pituitary adenomas, gliomas, germinomas, and meningiomas; space-occupying lesions that cause compression and destruction of the hypothalamic-pituitary region can impair gonadotrophin secretion. In adults, prolactin-secreting pituitary adenomas (prolactinomas) are the most frequently encountered and can cause functional HPG axis suppression by inhibition of GnRH secretion (as discussed in Section 4.4), or by mass-effect to directly disrupt pituitary gonadotroph function.

4.4 | Functional central hypogonadism, including hypothalamic amenorrhoea (HA)

4.4.1 | Description and definition

The stress of any acute illness, including surgery, burn injuries, myocardial infarction, stroke and sepsis have all been noted to suppress the hypothalamo–pituitary–ovarian axis and, when stress becomes prolonged as per any chronic illness, suppression of GnRH-induced gonadotrophin secretion becomes entrenched. In females, this form of functional CH is commonly known as HA and most commonly arises from a state of relative energy deficit (restricted nutritional intake and/or excessive exercise leading to low fat mass and hypoleptinaemia).

High-achieving and perfectionist personality traits and sleep deprivation are also known to be associated, but there are clearly individual predisposing factors that determine why women with apparently similar body habitus and activity levels may be discordant for HA. South Asian women appear protected due to higher fat mass than Europeans with a similar BMI. Moreover, cohorts of women with HA are enriched with CHH-associated genetic variants compared with control populations, which may increase their susceptibility to HA.[78,79]

Although none of these hormones can be measured in clinical practice, HA fundamentally results from hypoleptinaemia due to low fat mass, which in turn reduces hypothalamic Kp and GnRH secretion. Ovulation may be restored by stimulating or replacing using exogenous gonadotrophin injections (FSH with LH) or pulsatile GnRH (although, as previously stated, this is currently not commercially available).

Neuroendocrine networks are intact and so the obstacle to pulsatile GnRH secretion relates to an excess of inhibitory signals and/or insufficient stimulatory inputs to higher centres—particularly the infundibular nucleus. Removing or addressing the underlying cause for the signalling disturbance (reversible upon recovery from or remission of the underlying disease process, or improved nutritional status and fat mass, where achievable) allows normal function of the HPG axis to resume with restoration of normal ovarian hormone secretion, menstruation and fertility.

4.4.2 | Hypothalamic amenorrhoea and extremes of BMI

In HA, physical, psychological, or nutritional stressors result in suppression of ovulation and menses,[80] restricted food intake and exercise being a cornerstone of the disease process. Most women and girls presenting to a gynaecologist or endocrinologist with HA will not have an active eating disorder such as anorexia nervosa (AN), although many will have disordered eating or a history of an eating disorder. The management of HA is discussed further in the section on Holistic patient management.

Unlike women with AN, who typically have profoundly low estradiol levels below the reliable limit of detection for immunoassay, a much wider range of estradiol concentrations is observed in HA. In studies that excluded women with the most profound disease bordering on AN, or in which predetermined estradiol levels were specified (*e.g.* < 100 pmol/L or <30 pg/mL), mean estradiol concentrations recorded in HA comprised 142 ± 15,[81] 150 ± 23,[82] 120 ± 14.3,[83] and 125 ± 150 pmol/L.[84] These concentrations are in line with those recorded in larger series of women with lactational amenorrhoea from exclusive breast-feeding: 227.6 pmol/L,[85] 224 ± 27 pmol/L (<180 days) and 156 ± 10 pmol/L (> 180 days),[86] and 128.5 ± 14.2 pmol/L.[87] Although the wide variability in levels observed in some series is an important consideration. taken together, these findings informed the 200 pmol/L threshold, which we adopted as described in the Introduction (Section 2), that should prompt serious considerion of an FH diagnosis in a woman with amenorrhoea.

Although directly comparative data are lacking, the female HPG axis is more vulnerable to the effects of energy deficit, exercise and/or low fat mass[88] for obvious evolutionary reasons.[88] In contrast,

women seem to be less prone to HPG suppression with obesity[89] or glucocorticoid excess (Cushing's syndrome),[90] in which anovulation more commonly results from ovarian hyperandrogenism in the less severe cases.

4.4.3 | Iatrogenic central hypogonadism

Like hypoleptinaemia, hyperprolactinaemia suppresses the HPG axis by inhibiting Kp secretion from the infundibular nucleus (human analogue of the rodent arcuate nucleus).[91,92] Raised serum prolactin concentrations may result from physiologic (e.g. stress, illness, sleep deprivation, or lactation), pathophysiologic (i.e. prolactinoma) or iatrogenic causes (i.e. dopamine antagonist drugs). Notably, dopamine negatively regulates prolactin secretion while serotonin has a stimulatory role. Thus, both dopamine-antagonist antipsychotic drugs and serotonergic anti-depressants can cause elevated prolactin levels and may induce hypogonadism.[93]

It may be feasible to achieve a normal prolactin level and restore menstrual cyclicity by amending long-term psychiatric drug treatment, for instance with the introduction or substitution of newer antipsychotic drugs such as aripiprazole, in which case no further investigation or treatment is required. However, pituitary MRI and full assessment of anterior pituitary function may be required if there is any doubt. UK mental health guidelines mandate monitoring prolactin levels at baseline and regularly during treatment in patients on long-term antipsychotic drugs, irrespective of symptoms, which generates a vast number of high prolactin levels that only exceptionally rarely lead to the new diagnosis of a pituitary lesion. Having first documented the pretreatment menstrual pattern and prolactin level, we instead recommend an approach based upon identifying relevant clinical symptoms and signs (e.g. secondary amenorrhoea, vasomotor or urogenital symptoms or sexual dysfunction) at the annual medication review. If any are identified or there is any doubt, the biochemical signature of CH should be screened for, in order that women with hyperprolactinaemic CH do not remain undiagnosed and untreated.

Opiates are another common cause of functional CH, whether used for chronic pain management or as a result of narcotic addiction. Over the last two decades their manufacture and prescribing has greatly increased in developed nations, accompanied by growth in the market of illicit opioids and the rise of heroin-related treatment-demand.

GnRH analogues are used to suppress endogenous HPG activity in women with endometriosis and fibroids, but when continued for longer than 6 months, add-back combined HRT should also be prescribed to prevent the consequences of CH.

Depo-Provera® is a convenient, popular and effective form of contraception (or treatment for menorrhagia), which typically results in amenorrhoea and a minor reduction in serum estradiol concentrations. However, a minority of women develop more profound HPG axis suppression, which may remain undiagnosed due to amenorrhoea being an anticipated effect. We therefore recommend brief annual clinical screening (every fourth injection) by the administering nurse for vasomotor symptoms, vaginal dryness, dyspareunia or reduced libido; followed by biochemical confirmation if needed.

5 | LESSONS FROM THE MENOPAUSE IN RELATION TO HRT IN YOUNG WOMEN

In 2022, the SfE, British Menopause Society (BMS) and Royal College of Obstetricians and Gynaecologists (RCOG) published a joint position statement on the management of the menopause and menopausal transition.[94] We list below those elements having direct relevance to younger women with FH, along with our additional comments and review of the literature.

HRT is considered as the first-line intervention for the prevention and treatment of osteoporosis in women with both early menopause (40–45 years old) and POI. Potential adverse effects and key special situations in relation to HRT are covered in greater detail in Section 10, but are also briefly outlined for clarity here, so as to emphasise the debt that we owe to studies performed on postmenopausal women.

Studies of post-menopausal women show increased incidence rates for breast cancer in all HRT groups compared to those who never used HRT.[95] Estrogen-alone HRT is associated with a far lower risk of breast cancer than combined HRT, but should only be used in those women lacking a uterus due to the risk of endometrial hyperplasia or even carcinoma with long-term unopposed estrogen. The risk of developing breast cancer is duration- and possibly dose-dependent and may vary with the type of progestogen used.

HRT including micronised progesterone or dydrogesterone carries a lower breast cancer risk than medroxyprogesterone acetate, levonorgestrel and norethisterone acetate.[96,97] The biological basis may be that progestogens such as micronised progesterone or dydrogesterone have proapoptotic or neutral effects on breast epithelial proliferation, whilst medroxyprogesterone acetate and androgenic progestogens have a proliferative effect.[96] There is no evidence of an effect of the route of administration of estradiol on breast cancer risk.

In postmenopausal women, sequential HRT (sHRT) is associated with a slightly increased risk of ovarian cancer,[98] though the lifetime risk of ovarian cancer is low, and UK MHRA data suggest only one extra case of ovarian cancer per 1000 HRT taking it for 10 years (and none for 5 years' use).[99] In contrast, continuous combined HRT (cHRT) reduces the risk of endometrial hyperplasia and cancer below background rate, but is associated with a relatively higher risk of breast cancer than sHRT.[100]

Transdermal administration of estradiol is unlikely to increase the risk of venous thromboembolism (VTE) or stroke above that seen in non-users, being associated with a lower risk than oral administration (principally of ethinylestradiol—EE and conjugated equine estrogens—CEE). The transdermal route should therefore be considered as the first choice route of estradiol administration in women with related risk factors.

Low-dose vaginal estrogen preparations should be prescribed to women experiencing genitourinary symptoms despite taking systemic HRT in doses sufficient to control their symptoms. All vaginal estrogen preparations (pessaries, creams and slow-release vaginal rings) have been shown to be effective in this context and there is no requirement to provide additional progestogen as low-dose vaginal estrogen preparations do not result in significant systemic absorption or endometrial hyperplasia.[101]

Testosterone supplementation can be considered in postmenopausal women with low sexual desire if systemic HRT, with or without progestogen, resulting in adequate estradiol levels has not been effective.[102] However, BMS guidance does not specify what constitutes an 'adequate estradiol level' in a postmenopausal woman taking HRT. The impact of testosterone treatment on cardiovascular risk in postmenopausal women remains to be established.[103]

Moreover, before making a general diagnosis of low sexual desire, it is important to first identify and treat other barriers to enjoyable sex, such as subtherapeutic HRT doses, dyspareunia arising from vaginal dryness and non-endocrine psychosexual factors. No female-specific testosterone preparation is currently available in the UK, and thus a very low dose (e.g. approximately 10%, 5 mg/day) of a male preparation may be used. Other potential therapies for low libido in women that warrant further study, but cannot be recommended as yet, include bremelanotide[104] and kisspeptin.[105]

6 | EVIDENCE FROM STUDIES OF TRANSGENDER WOMEN

Hormone replacement therapy for transgender women (TW) is used across the age span from the late teenage years through to old age, but with the majority of individuals in the age range corresponding to the period of normal reproductive life in cis-gender females, and with guidelines emphasising the importance of ongoing clinical and biochemical monitoring. The effects of estrogen therapy in this situation may thus provide additional insights into the optimal management of sex hormone replacement in cis-women with hypogonadism, complementing data arising from the study of postmenopausal women.[106–109]

Over the past 2–3 decades, improvements to the medical management of TW have contributed to a dramatic reduction in the risks of estrogen-associated stroke, cardiovascular disease and VTE, that were unacceptably high in earlier cohorts. In part, this may reflect general medical progress in delivering more effective smoking-cessation, lipid-lowering, hypertension- and weight-management interventions, but there are nevertheless three key lessons to be learnt from the direction of travel over this period in respect of HRT prescribing.

First, there is a consensus that the estradiol dose requirements for transgender women are likely to be higher than those contained in even the higher-dose products licensed for postmenopausal women. It should, however, be remembered that the therapeutic aims in transgender women may differ from HRT in cis-gender women.

Second, there has been a wholesale switch (particularly across Western Europe) to prescribing native estradiol, rather than EE or CEE, with a preference for the transdermal route in older or obese individuals and others at greater risk of arterial or venous thrombosis.

Third, there is consensus that treatment doses should be guided by biochemical monitoring, something that is not yet firmly recommended in respect of FH. Clinicians are advised to achieve serum estradiol concentrations within a sensible target range (typically 300–600 pmol/L in the UK), to reflect average follicular phase levels in younger cis-gendered women.[110] This empirical strategy aims to avoid both over- and under-treatment.

In summary, given the limited information relating to younger women on the safety and efficacy of estrogen replacement, analogous data relating to the treatment of trangender women can provide valuable insights into estrogen replacement from large cohorts of younger people. Although we should be cautious in generalising these data, they support the contention that replacing estradiol to the target range maintains bone health, induces and maintains female secondary sexual characteristics and does not increase thromboembolic risk in those younger that 37.5 years old.[111,112]

7 | LESSONS FROM HRT IN TURNER SYNDROME (TS)

7.1 | Why is TS different from other forms of POI?

HRT in women with Turner Syndrome deserves individual consideration as this subgroup of women is predisposed to other co-morbidities such as congenital cardiovascular and renal anomalies, aortopathy, risk of liver dysfunction, propensity to autoimmune disease, metabolic dysfunction, hypertension from a younger age, increased cardiovascular risk, impaired bone health and increased mortality (even more so than women with 46,XX POI) compared to the background female population.[113–116]

The spectrum of clinical features is variable, depending at least in part on the underlying karyotype and presence of mosaicism, ranging from 45,X, to structural abnormalities and presence of Y chromosome material, to mosaicism with a predominance of 46,XX. Thus, while the majority of girls will have primary amenorrhoea and therefore potential effects on, for example, achievement of peak bone mass, a proportion will have spontaneous puberty and regular periods.

7.2 | Effects of HRT in TS

Whilst most information regarding HRT in all women with POI is pertinent to women with TS, the reader is referred for a comprehensive discussion of literature and recommendations to the 2017 international clinical practice guidelines from the International Turner Syndrome Consensus Group.[42] This advised monitored estrogen replacement for most women with TS, with transdermal estradiol as first line therapy and with recommendations on progestogens in line

with our discussion above. Draft updated guidance currently out for consultation (March 2024) includes the recommendation to optimise uterine growth in puberty and bone health in adulthood, by achieving target range serum estradiol concentrations of 350–500 pmol/L.

7.3 | HRT and cardiovascular risk in TS

Much of the data on HRT for TS are drawn from older observational small studies, for relatively short duration and using variable formulations of estrogen. It is reasonable to conclude however that there are probable beneficial effects of estrogen replacement on blood pressure[117,118] and lipid profile.[119] Recent meta-analyses and systematic reviews highlight inconsistent studies lacking hard end-points, but showed transdermal estrogen to be associated with lower HDL cholesterol compared with oral estrogen replacement, albeit with no or slight differences in total or LDL cholesterol, or in triglycerides.[120–122] However, as discussed in Section 7.4, these studies have generally considered oral estrogens as a single entity, not differentiating between CEE (which is no longer recommended in TS),[122] EE and 17β-estradiol. Nevertheless, a comparison of pharmacokinetics and pharmacodynamics of oral and transdermal estradiol in girls with TS (mean age 17.7 years) compared with normally menstruating girls showed that transdermal estradiol more closely approached the average follicular phase estradiol concentrations for healthy young women,[123] although lipid concentrations did not differ significantly and glucose concentrations did not change.

Women with TS have increased carotid artery intima media thickness (IMT), a surrogate marker of CV disease risk, compared with control women. However, incremental doses of oral estradiol over 12-week intervals from 1 to 4 mg daily achieved dose-dependent reductions in IMT without any adverse impacts on blood pressure.[124] These data raise the possibility that achieving optimal CV disease protection in TS might require higher estradiol doses than in standard postmenopausal HRT, though confirmatory long-term studies are lacking.

Danish registry data including large numbers of women with TS support the beneficial metabolic effects of estradiol-based HRT in women with TS. A study comparing women with TS with age-matched female controls showed significantly lower use of antihypertensive (HR 0.5) and antidiabetic drugs, and significantly reduced hospitalisation rates for stroke and osteoporotic fracture in the 45,X karyotype subgroup receiving estradiol-based HRT, compared with those not receiving HRT. This study also reported a reduction in incidence of stroke in the HRT-treated group (HR 0.17) across all karyotypes and a trend toward lower mortality among current HRT users.[116]

7.4 | Bone density and fracture risk

TS is associated with low bone density and increased risk of fracture, although assessment of bone fragility is challenging in TS both in terms of short stature and investigating younger age women.[42] Moreover, the factors underpinning the increased risk of fragility fracture in TS are more complex than in other forms of POI, comprising chromosomal abnormalities, nutritional deficiencies from associated coeliac disease and inflammatory bowel disease, and an increased risk of falls due to impaired hearing, balance, or spatial coordination, in addition to the effects of estrogen deficiency.

Women with TS have lower baseline bone mineral density (BMD) at all sites, which may reflect reduced peak bone mass achieved during adolescence in addition to an increased rate of bone loss in adult life. Nevertheless, adequate HRT combined with a healthy lifestyle has been shown to maintain BMD.[125] A recent meta-analysis and systematic review included randomised controlled trial (RCT) and cohort studies in women aged under 40 years with TS;[120] 25 studies for qualitative and nine for quantitative meta-analysis. The analysis was limited by variable duration, type of HRT, and age of women; only one study included fracture as the endpoint while the remainder relied on bone density. However, it was concluded that HRT improves BMD in women with TS, with further data required to assess optimal route of administration and timing. Crucially, the data supported the use of 17β-estradiol rather than synthetic EE (as contained in most forms of COC) for bone health in TS.

Although transdermal 17β-estradiol is currently recommended by International Guidelines,[42] there are few supporting data in TS and the key take-away lesson may instead be to use 17β-estradiol (whether oral or transdermal), rather than EE or CEE. Indeed, subgroup analysis of an open label, 12-month randomised controlled crossover trial of transdermal HRT (mean estradiol patch dose 137.5 mcg) versus a COC in POI (including seven women with TS) found a greater benefit on lumbar spine BMD, mediated by increased bone formation and decreased bone resorption.[126]

Whether the dose of estradiol is important to BMD is unknown; a 5-year prospective double-blind randomised controlled trial of standard dose (2 mg) versus high dose (4 mg) estradiol in young (mean age 19.2 years) women with TS showed similar increases BMD and reduced bone turnover markers in both groups, although lean body mass increased to a significantly greater extent in the higher dose group ($p = .02$). This finding is of uncertain significance, but is potentially beneficial across a range of long-term health domains.[127]

It is clear however that earlier recognition and treatment of estrogen deficiency, avoiding prolonged breaks in therapy throughout the reproductive age range, is crucial for optimising bone health in TS.[128] Population data from the recent Danish registry study of 329 women with 45,X TS confirmed the high prevalence of osteoporosis in women with TS, but found a significantly reduced risk of fragility fracture in current HRT users compared with non-users.[116]

7.5 | HRT and liver anomalies in TS

Abnormalities of liver biochemistry in TS are common, affecting approximately 50% of TS women (range 20%–80%),[129] with an increased incidence of NAFLD (nonalcoholic fatty liver disease, now often known as metabolic dysfunction-associated fatty liver disease - MAFLD), nodular regenerative hyperplasia and even progression to

cirrhosis in a small number of women.[130] Estrogen deficiency is associated with increased hepatic cell fat content,[131] and treatment with 17β-estradiol (whether oral or transdermal) has been shown to improve liver biochemistry.[129,132] A large registry study including 1156 women with TS focussed on the effects of HRT in the 45,X subgroup ($n = 329$), finding no impact on gastrointestinal disease and anaemia, but a trend towards a beneficial effect on liver disease.[133] A more recent study found a benefit of oral estradiol in women with steatohepatitis.[134] International Guidelines thus recommend continuing HRT in TS women in the face of abnormal liver biochemistry, with supportive evidence from studies showing improvement or even normalisation of liver biochemistry with adequate 17β-estradiol therapy.[135] This further demonstrates the importance of continued adequate HRT for women with TS, at least until MAM.

7.6 | Other issues and overall conclusions in relation to HRT in TS

Possible beneficial effects of estrogen replacement on aspects of neurocognitive function have been reported for girls and adolescents with TS,[136,137] but there are a lack of consistent data in adults.[122]

Current data suggest estrogen replacement is safe for the vast majority of women with TS. During a 20-year follow-up of 1,156 women with TS there was a very low incidence of breast cancer that was not increased by HRT.[116,138] Older cohort and population studies confirm the lack of increase in hormone sensitive cancers, although some but not all, have also reported an increased meningioma risk.[139] The large registry study of hospitalisation, mortality and prescriptions in women with TS was relatively reassuring, with no increase in risk of VTE,[116] although older studies had identified a potential pro-coagulant serum profile.[140] The Danish registry identified a trend towards increased risk of ischaemic heart disease with HRT compared with nontreated and a nonsignificant risk of dyslipidaemia, but the number of events was small.[116]

Patient satisfaction and perspectives on hormone replacement therapy highlight important considerations when treating women with TS.[141] Out of 346 women with TS who were diagnosed at mean age 10.7 years, the majority were given information on HRT as expected in childhood/adolescence. Approximately two-thirds of women (62%) were broadly satisfied with the age of starting treatment (mean 15.5 years), but one-fifth of women would have definitely preferred to commence earlier. The majority were satisfied with the information they received about treatment, although over 20% were dissatisfied with the amount of information about treatment choice, risks and side-effects.

The clinical practice guidelines for TS[42] recommend long-term HRT following induction of puberty until at least MAM, assuming no breaks in therapy, but usually beyond if there have been prolonged breaks in HRT. Many clinicians with expertise in the area recommend higher 17β-estradiol doses in younger women and lower doses in older women, but evidence to support this is limited or absent. Furthermore, debate continues about assessment of adequacy of replacement,[113,142] although a recent Danish study found comparable mean [95% CI] serum estradiol concentrations in HRT-treated TS women (125.5 pmol/l [0.01–1988]) and early follicular phase eugonadal women (136 pmol/l [0.01–2989]) ($p > .5$).[143] Progesterone replacement is important to protect from endometrial hyperplasia and although the optimal formulation and dose regimen is not clear, the notable lack of endometrial malignancies identified in any case series is reassuring. Women with TS have reduced levels of testosterone and other androgens, but the effects of androgen supplementation in TS are yet to be well studied.[113,143]

Whilst a significant proportion of women with TS are delayed in diagnosis, or undergo pubertal-induction relatively late, and some may never be detected, it is imperative that all women with a diagnosis of TS and POI receive appropriate 17β-estradiol replacement therapy. It is therefore highly concerning that the Danish Cytogenetic Central Registry (1960-2014) identified that 13.6% of women with 45,X TS had never received HRT.[138]

8 | INFORMING PATIENT CHOICE FOR HRT

It is important to recognise that when the cause of FH cannot be reversed, there is no suitable alternative to HRT, or a 'no treatment' option for this patient group that offers remotely equivalent health benefits, and that prolonged estrogen deprivation risks significant health problems.[96] The initiation of HRT treatment in FH usually involves a review of the individual factors influencing the potential risks and the benefits of treatment, from their personal medical history, family history, smoking history, clinical examination and results of investigations.

However, there are relatively few absolute contraindications to HRT for FH, with the main one being a personal history of hormone sensitive cancer. Whether this should also hold for women with triple receptor negative breast cancer has been questioned.[144] However, ER-negative breast cancer is still associated with an up to 30% increased risk of ER-positive contralateral breast cancer and an 8% risk of ER-positive metastatic disease,[145] and caution is thus advised until more evidence emerges.

The other risk factors relating to HRT in older postmenopausal women, or COC use in women of reproductive age probably do not apply to the prescription of HRT in FH. Personalised approaches to recommend specific types and routes of estrogen and progestogen to optimise the safety of HRT are based on extrapolated data and expert consensus, rather than higher quality research evidence in this specific patient group. Finally, an increase in relative risk may only have a slight effect on a small absolute risk of adverse outcomes in younger women.

Treatment should be re-assessed periodically once established on treatment (by convention, annually). Individual patient factors may evolve, such as fertility wishes, breakthrough vasomotor or genito-urinary symptoms indicating under-replacement of estrogen, and as new evidence accumulates with the passage of time. This is also an

opportunity to ensure that those taking separate preparations of estrogen and progestogen understand the importance of the progestogen to provide endometrial protection, and to enquire after any unscheduled bleeding in those with a uterus.

Women with FH are conventionally advised to take hormone replacement until MAM and, thereafter, according to their individual priorities and characteristics as per menopausal HRT. However, in practice, they frequently report prolonged delays in diagnosis and initiation of treatment, along with prolonged interruptions to their HRT prescriptions associated with drug unavailability, delayed prescriptions and life events (intercurrent illness, moving to another city or country, or even getting registered with a new doctor) (Box 1).[41,70,138] In these women, the individualised risk assessment at MAM should take these 'lost years' into account, particularly if bone density remains compromised, and potentially supporting continuing HRT until the upper age of normal menopause or even slightly beyond.

Having provided as much information as possible to support a woman with FH to accept HRT and make an informed choice about type and route, it is important to acknowledge the insufficiency and uncertainty of the evidence base, particularly where relative risks or benefits are likely to be marginal. The woman's personal choice about what is right for her at that time should be respected, for example in relation to the route of the estrogen and progestogen. This will increase the likelihood of concordance and satisfaction with the treatment plan. If treatment is declined, it is important that this decision is treated with respect and efforts made to ensure the decision is informed, including exploring any reasons given. The decision can be revisited at follow-up and after any tests monitoring the adverse effects of FH, for example on bone density.

9 | TYPES OF HORMONE REPLACEMENT AVAILABLE

9.1 | Routes, doses and regimens for HRT administration

The preferred type of estrogen is 17β-estradiol to provide physiological replacement and allow serum levels to be measured, if necessary. Almost all currently available HRT preparations contain estradiol and are free of prescription charges in England for women with CH and HA as these could be construed as a form of 'pituitary disease', but not for those with POI unless they have another personal or medical reason for exemption. Doses are discussed in Table 1. In contrast, most large studies on HRT were undertaken in postmenopausal women, and largely utilised older and more prothrombotic HRT preparations, so the results may not necessarily be extrapolated to younger women taking modern preparations, particularly in respect of their adverse effects.

The term 'bioidentical hormones' is sometimes used to describe preparations chemically identical to hormones synthesised in the premenopausal ovary (although derived from plant sources), but is also used commercially to market unlicensed products such as customised compounded hormone preparations or progesterone creams. The use of these therapies is not recommended because of concerns related to their purity, potency, safety and lack of clinical trial data. The potential benefits of bioidentical hormone therapy (over synthetic analogues of estradiol and progesterone) can be achieved using conventional licensed products, available through standard prescribing, without having to resort to compounded products from specialist pharmacies.

Women with a uterus require progestogen for endometrial protection, which is administered for 12–14 days per monthly cycle in sHRT and daily in cHRT regimens. sHRT comprises continuous estradiol with intermittent progestogen, approximately following the normal physiological pattern, albeit without significantly varying estradiol levels across the cycle. It minimises progestogen exposure to the 12–14 days required for endometrial protection. cHRT gives continuous estrogen and progestogen in a balanced formulation. This aims to maintain a continuously thin endometrium, albeit with a tendency to breakthrough bleeding in younger women even with good adherence.

Commercially available combined preparations deliver HRT in fixed doses through oral or transdermal patch formulations. Alternatively, estradiol and progestogen can be delivered separately, which allows for tailored doses of estradiol and a choice of progestogen. Estradiol can be delivered alone as oral tablets, transdermal patches, gels or a spray. Progestogen can be delivered alone as oral tablets, as part of combined HRT patches, or through a 52 mg levonorgestrel releasing IUS. Vaginal preparations of progesterone are not licensed for endometrial protection as part of an HRT regimen, but there is reasonable experience for endometrial protection in off-label use and, as such, it is mentioned in BMS guidance.[153]

A range of progestogens are used for HRT (Table 2), with the preferred type being less certain than is the case for estrogens. Natural progesterone is available in micronised form and is best taken at bedtime as it may be associated with nausea or sleepiness. Synthetic progestogens are used in all combined HRT and all COC products, albeit dydrogesterone is a progesterone stereoisomer and thus structurally almost identical. Medroxyprogesterone acetate and norethisterone provide greater endometrial protection, but are also prothrombotic, and the former was recently associated with an increased risk of meningioma with use for longer than 1 year, albeit not a great as with cyproterone acetate.[154] Therefore, as first line treatment, we recommend micronised progesterone, dydrogesterone, or levonorgestrel IUS.

It has been suggested that the dose of the progestogen should be proportionate to the dose of estrogen to ensure adequate endometrial protection. Thus, women who require higher doses of estradiol than 2 mg oral, 100 mcg patches, 2 mg gel or 3 sprays may require a higher dose of progestogen than is contained in standard combined preparations. While this makes intuitive sense, direct evidence to underpin this advice is lacking. Therefore, we propose more simply that, for younger women with a uterus (who may need to take HRT for four decades or more), the progestogen dose should be adequate to avoid the development of endometrial hyperplasia.

BOX 1 Perspectives from patients and support groups

Several themes emerged from these discussions, including some illuminating statements that we have quoted *verbatim*.

It is important for patients and healthcare professionals to remember that women with FH are taking HRT for long-term estrogen deficiency from a young age, which is very different to the situation of postmenopausal women. Therefore, the negative press that surrounds HRT, which can be very confusing and misleading in a lot of ways, does not relate to women with FH.

Late diagnosis beyond expected pubertal age causes the feeling of being left behind, along with longer-term issues of body confidence and low self-esteem. Psychological support would be really helpful to those of us experiencing these problems, but there is no clear pathway to access it. Peer-support from support groups and talking to other patients is the best alternative.

'*As a teenager, my lack of periods and puberty was ascribed for far too long by doctors to being a late bloomer; now that I am in my 40s, doctors assume that I am menopausal, which remains frustrating. Maintaining contact with your specialist and being as well-informed as possible is the key to success in managing this condition across life's journey; consider taking someone else to appointments with you, as there may be a lot to remember*'.

With combined HRT there is a need to explain what each hormone (estrogen and progestogen) does along with the risks and benefits, and there is a need to repeat this information at subsequent appointments; re-emphasising the benefits of replacing missing estrogen and the protection it offers to younger women, particularly those who are most vulnerable.

Many women with FH believe that the estrogen may be affecting their moods, when in reality it is far more likely to be the progestogen, and they should not give up, but persist trying as many different HRT options as necessary to find the one that suits best, including levonorgestrel IUS; potentially even being fitted under general anaesthesia if they are not sexually active.

Around a quarter of women with CH have never been sexually active [146] and would appreciate advice on whether going for cervical smear tests is really necessary. By contrast, many women who are sexually active frequently experience vaginal dryness, but may feel uncomfortable bringing up the issue themselves.

Where a COC is being prescribed as HRT, it is crucial to ensure that this fact is recognised in primary care and by their community pharmacist. This is because patients who develop obesity, migraine or hypertension report getting pressured to switch to progestogen-only contraceptives, which would leave them with untreated estrogen-deficiency unless they stand their ground.

'*I'm on the COC as HRT and am treated by the nurse the same as a person using it for contraception, so I'm constantly having my weight discussed with me and the threat of not having it prescribed without a suitable alternative HRT being offered*'.

Younger women with FH report being on the receiving end of inappropriate and ill-informed comments by healthcare professionals in the community, such as

'*You're far too young to be taking HRT*'

'*You've already been taking this HRT for over 5 years, so will now need to stop due to the risk of breast cancer*'.

They wished their doctors were more aware of how the condition affected their mental health and how careless comments could impact on this. Women with organic FH and minimal possibility of achieving natural parenthood can become understandably distressed by 'tick-box' questions during medication reviews in the community, such as '*could you be pregnant?*', and may also infer from this that the healthcare professional does not understand the nature of their condition or why they are taking this particular medication.

Many women report being prescribed HRT only a month at a time, rather than quarterly as per national guidance, which drives up the cost for those who pay NHS charges in England, creates greater inconvenience in terms of having to make 12 telephone or online requests per year and, overall, greatly increases the risk of experiencing significant breaks in treatment.

Women with POI (including Turner syndrome) cannot understand why they should have to pay for HRT scripts in England, whereas women with central hypogonadism or HA are exempt under the category of 'pituitary disease'.

Women with FH also report difficulties in ensuring that HRT is included among their 'repeat prescription' drugs; needing instead to be individually requested by name each time. This is hard to fathom given that women with congenital FH may need to be take HRT for four decades.

Patients do understand that pharmacies sometimes struggle to source their usual form of HRT, but are unhappy with being sent away without anything at all, rather than the Pharmacist being empowered to dispense a reasonable substitute preparation on the spot.

'*A lot of us struggle getting HRT supplied which complicates it all to the point where we have to try and be one step ahead at all times; you wouldn't ask a diabetic to go without insulin, or an epileptic without seizure medication? Yes, it's not life threatening if we go without, but it's extremely miserable!*'.

Patients would like greater consistency of care, like seeing the same doctor.

'*Overall my annual appointment feels about right, but if you want me to change to patches or change dosage then I should have at least a phone follow up to check it's going OK and, if not, then to discuss options, rather than having to wait until next year's appointment*'.

In addition, the 40 plus Turner Syndrome Support Society booklet has the following insights[147]:

'It is important to discuss with your TS specialist consultant when is the right time for you to come off HRT, taking into account, bone density, age, general health etc. and using the results from all the health checks you've been having over the years. This will guide you to making the right decision for you'.

'It is important to remember that a woman without TS will go through the menopause in her early 50s but would then possibly go on to use HRT to help her through it. This can take anything up to 5 years so you could, potentially, be looking at taking HRT into your late 50s with the agreement of your specialist. You may feel more comfortable coming off estrogen gradually rather than just stopping suddenly and completely'.

TABLE 1 Preparations of 17β-estradiol and approximate equivalences.[148–151]

Patch (mcg/24 h)	Gel sachet (mg/day)	Gel pump (0.75 mg/ actuation) No. actuations	Spray (1.53 mg/actuation) No. actuations	Oral (mg/day)
Lower dose menopausal HRT products are probably not suitable for younger women with FH				
25	–	–	1	0.5
50	0.5	1	2	1
75	1	2	3	1.5
100	1.5–2	3–4	–	2
125–150	2.5	–	–	3
175–200	3	–	–	4

Note: Where use of estradiol is outside product license for menopause HRT, consideration should be given to increasing progestogen dose to ensure endometrial safety.

Thus women using sHRT having regular withdrawal bleeds without any unscheduled bleeding can be assumed to be achieving adequate endometrial protection, as do women with a 52 mg levonorgestrel IUS. Similarly, in older women with premature or normal perimenopause, the absence of breakthrough bleeding or spotting is conventionally taken to indicate that the endometrium is not abnormal. However, there are only limited long-term endometrial safety data relating to the use of cHRT spanning several decades. Unscheduled and unexplained bleeding in younger women taking cHRT still needs investigation to rule out pathology.

Transdermal estradiol is considered the metabolically 'best' route in respect of serum triglycerides, VTE and stroke risk, although its predominant advantages for the latter two risks may be over EE and CEE, rather than oral estradiol, which is suitable for most younger women. However, transdermal estradiol is definitely preferred for those with obesity, migraine, hypertension, hypertriglyceridemia or those at higher risk of VTE. Estrogens may interact with the metabolism of anticonvulsants, so clinicians are advised to liaise with the prescribing neurologist before initiating therapy, and again the transdermal route is preferable.

Transdermal estradiol is available as gel, patch, or spray. Progestogens suitable for endometrial protection are available orally (micronised progesterone, medroxyprogesterone acetate and norethisterone—dydrogesterone is only available combined with estradiol in the UK, but singly in many other countries); as a norethisterone or levonorgestrel patch combined with estradiol, or levonorgestrel IUS. The Mirena® IUS is licensed in the UK for 4 years for this indication, however the Faculty of Sexual and Reproductive Healthcare, Royal College of Obstetricians & Gynaecologists and British Menopause Society support the use of any 52 mg levonorgestrel IUS for endometrial protection up to 5 years.[155]

HRT products are manufactured in limited dose ranges. Standard doses at the higher end of the dose range are 2 mg oral estradiol (lower dose: 1 mg), or 100 mcg transdermal estradiol patches (lower doses at 25, 37.5, 50 and 75 mcg). Even the higher dose products were formulated at the lowest effective doses to suppress vasomotor symptoms in menopausal women and may thus not be adequate for younger women. Unfortunately, the two available pure-transdermal cHRT products (estradiol 50 mcg with norethisterone 170 mcg or levonorgestrel 7 mcg in a single patch) may be inadequate for the majority younger women with FH (Table 1),[148] and thus two patches will usually need to be worn together, in our opinion.

The COC is widely available and is free of prescription charges across the whole of the UK, and also provides contraceptive cover if required. The COC usually contains ethinylestradiol (EE) which is a synthetic estrogen, although products containing native estradiol and having fewer 'blank' days are now more widely available. As outlined in Sections 8 and 14, and also reviewed elsewhere,[156] an EE-based COC is less suitable than HRT for long-term use due to greater risks of hypertension (patients must undergo regular blood pressure monitoring in primary care) and VTE, uncertainty as to dose-equivalence at the tissue level and the impossibility of doing any biochemical monitoring.

TABLE 2 Progestogens.[11,152]

Progestogen	Dose and route	Usage notes
Micronised progesterone	200 mg oral or 100–200 mg vaginal pessary; 12–14 days per month	No direct evidence for breast cancer risk[97]
		Drowsiness and dizziness
		Less good cycle control
		More frequent breakthrough bleeding
	100 mg oral, or 100 mg vaginal pessary daily	Neutral in respect of VTE and cardiovascular risk
Dydrogesterone = progesterone stereoisomer, where hydrogen atom at carbon 9 is in the β position and methyl group at carbon 10 is in the α position; the reverse of progesterone structure	10 mg oral for 12–14 days per month	Currently only available as part of combined HRT
		High selectivity and lacking glucocorticoid/androgenic activity
	5–10 mg oral daily	Neutral in respect of VTE and cardiovascular risk
		Neutral on blood pressure, body composition, glucose, lipid metabolism and endothelial function markers
Medroxyprogesterone acetate	10 mg oral for 12–14 days per month	Widely available and cheap
	5 mg oral daily	Mild androgenic and glucocorticoid-like actions on lipid and glucose metabolismUpregulation of thrombin receptor (pro-thrombotic)
Norethisterone acetate	5 mg oral for 10 days per month	Androgenic activity; possibly more likely to cause acne, but comparative data are limited
*No data relating to transdermal administration	1 mg oral daily	
	As patch (with estradiol 50 mcg), 170 mcg/24 h	Best endometrial protection
		Risk of hepatotoxicity*
		Pro-thrombotic*
Levonorgestrel	52 mg intrauterine device; needs changing after 5 years	Limited systemic exposure
		Insertion without general anaethesia may be painful or challenging for nulliparous or hypogonadal women

9.2 | Monitoring HRT

In the absence of more robust evidence, we advise that the available strategies to assess the adequacy of HRT include clinical assessment of symptom-control (although often not reliable for all forms of FH) and general well-being; serum estradiol concentrations, and DXA bone densitometry. Lack of withdrawal bleeding on sHRT may suggest an inadequate dose, reduced absorption or poor compliance in some women, but not all. This can be ascertained by more detailed questioning, measurement of serum estradiol levels and, potentially sonographic measurement of endometrial thickness.

Measurement of serum estradiol may be useful when patients taking HRT remain symptomatic despite a reasonable increased dose, when bone density fails to improve, when adherence is in doubt, or if concerned about excessive doses being used. Some, but not all, recommend routine annual serum estradiol measurement to ensure that a reasonable level is achieved, if necessary by supplementing estradiol to the basic regimen,[148,149] subject to the progestogen dose being adequate to prevent endometrial hyperplasia. To this end, the serum estradiol target ranges for UK transgender women (300–600 pmol/L) and in draft guidance from the International Turner Syndrome Society (350–500 pmol/L) substantially coincide. However, there is currently insufficient evidence to recommend whether serum estradiol testing or non-testing is better for efficacy and safety outcomes in women with FH.

Synthetic progestogens are not detected by progesterone assays, so measurement is not generally possible in guiding therapy, unless to check compliance in those taking micronised progesterone; neither is it useful to check concentrations of FSH, which are generally suppressed by COC, but are usually not by HRT. EE-based COC cannot be monitored biochemically as EE is not detected by estradiol assays, and there is no specific assay generally available.

9.3 | Trouble-shooting problems with HRT, including adverse effects

There have been national shortages of certain preparations of hormone therapy over recent years. When women are established on HRT, conversion to alternative treatment regimens can be difficult

as subject to marked interindividual variation, but Table 1 is a useful tool to facilitate these changes. The effectiveness of different therapies can also vary, so it is important that women are reviewed following any change in regimen and treatment adjusted accordingly.

It is not uncommon for women starting a new regimen to experience bleeding, or other hormonal side effects (breast tenderness, headaches, nausea, fatigue, mood change), although these issues usually settle without the need for further adjustment of the regimen. Breast tenderness is common on starting hormone replacement, especially after a long spell of amenorrhoea, but usually settles within 1–3 months. Otherwise, the estradiol dose can be reduced until symptoms subside and then gradually built up again.

Patients should be advised that breakthrough bleeding (BTB) on HRT is quite common, particularly in the first 3 months of a new regimen, and most frequently due to missed doses or misunderstanding of the regimen, but must be investigated if persistent beyond the first 6 months, or is newly occurring on established HRT. These situations should be investigated with bimanual and speculum examinations, high vaginal swabs, transvaginal pelvic ultrasonography and—if no recent negative result—cervical cytology. Depending on findings, endometrial biopsy may be required. If no other cause is found (or anyway if virgo *intacta*), then consideration should be given to increasing the dose of progestogen, changing the type (e.g. from micronised progesterone one giving greater endometrial protection, such as norethisterone), or extending the duration of progestogen in sHRT.

Some women suffer from progestogen intolerance, comprising bloating, fluid retention, acne, breast tenderness and 'premenstrual dysphoria' (mood swings, anger or weepiness). No specific investigations are required, but it may be helpful to chart cyclical symptoms. The dose of progestogen may need to be reduced, the specific progestogen changed, or the route varied, usually from oral to transdermal or intrauterine. For cyclical symptoms, a change from sHRT to cHRT or levonorgestrel IUS may be helpful.

10 | HOLISTIC PATIENT MANAGEMENT IN FH

In this section we discuss specific circumstances that commonly impact on patient management, including lifestyle measures to be recommended in parallel to HRT, as well as addressing concerns frequently expressed by patients relating to their baseline understanding of the benefits, risks and adverse effects of HRT. For those women with FH of prepubertal onset, detailed discussions by clinicians with their parents may have largely passed them by, or been forgotten with the passage of years. Not all will have transitioned from paediatric to adult services within the same healthcare organisation and, for some, their responsible paediatrician will have been an oncologist, rather than an endocrinologist. Therefore, time spent by clinicans or specialist nurses going over these issues 'again' in subsequent appointments is rarely wasted.

However, before proceeding further with this discussion, we should first acknowledge that a diagnosis of FH (and POI in particular) may have devastating psychological consequences on affected women, their families and loved ones; often due to the associated infertility, but also from feelings of a loss of a sense of womanhood or being prematurely aged. Many need psychological support, albeit the availability of this is patchy across the UK, and may benefit greatly from face to face or online peer-support via networks of 'expert patients'.

10.1 | Role of HRT in hypothalamic amenorrhoea (HA)

Women with HA have increased risks of disordered eating and history of eating disorders compared with other women with amenorrhoea.[157] HA is associated with reduced fat mass and lower circulating leptin and hypothalamic Kp levels that provoke reversible suppression of GnRH secretion.[158] It is therefore helpful to counsel the patient about the likely effects of their lean body habitus on reproductive health; such discussions need sensitive consideration, so that patients do not feel blamed or body-shamed.

Women with HA are more prone to mood disorders, have trouble coping with daily stresses, and endorse greater interpersonal dependence compared with normally menstruating women.[159] Small studies have suggested that psychological interventions may restore reproductive function in some women with HA. Menstruation was reported to return 12 weeks following a single session in nine of 12 women with HA who received a single session of hypnotherapy.[160] A small open-labelled randomised-controlled trial ($n = 16$) reported that cognitive behavioural therapy (CBT) was associated with a significantly higher rate of return of ovulation (6/8 women) compared with observation alone (2/8).[161] A further small study by the same authors suggested that CBT increases serum leptin and thyroid stimulating hormone (TSH) compared with observation.[162]

Although controlled studies are lacking, there is potential to restore reproductive function in women with HA and it is thus recommended that they moderate their exercise and attempt to achieve modest and gradual increments in weight. Therefore, a psychological approach with encouragement to support lifestyle-change is recommended at the outset, whether as sole therapy or in parallel to HRT. However, this may be extremely difficult for affected women to accept and so a sympathetic and non-judgemental approach is essential. Moreover, the availability of psychological interventions is limited in a public healthcare setting, and so may require self-funding by affected patients.

A significant proportion of women with HA find these changes to be unacceptable or otherwise impossible to achieve. Making adjustments to lifestyle may be particularly challenging where it could result in lack of income or other social adjustment. Therefore, under these circumstances, we recommend that women are offered HRT, whether as a bridging therapy pending the outcome of targeted interventions (e.g. behavioural and/or dietary) or potentially even until MAM if there is no resolution.[163] For reasons of bone and sexual health the recommendation to start HRT should not be generally be deferred for longer than 6–12 months beyond the initial discussion.

Contraception should also form part of discussions, with COC being considered as an alternative to HRT, as per Section 13.

The International Olympic Committee (IOC) does not favour the routine use of COC (or HRT) in athletes with HA,[164] who in any case benefit from direct access to expert multidisciplinary care from specialist sports physicians, dieticians, exercise physiologists and psychologists; generally undergo serial measurement of body composition by bioimpedance, and in whom high-impact exercise undoubtedly mitigates the skeletal impact of estrogen-deficiency. In our view, current sports medicine guidance pays too little attention to the impact of longstanding HA on athletes' sexual health (as opposed to just their performance and bone density) and is of limited applicability to the generality of women with HA in the community, who necessarily lack access to the multidisciplinary care available to high-level athletes.

In relation to women with profound Depo-Provera®-induced FH, substituting an alternative strategy to manage menorrhagia or deliver contraception, such as the combined oral contraceptive pill (COCP) or a hormonal IUS, will usually be more appropriate that starting HRT. However, drug substitution or elimination may be significantly harder in respect of opiate- or drug-induced hyperprolactinaemic FH, in which case HRT is indicated where these are unlikely to be withdrawn within a reasonable timeframe.[165–167]

10.2 | Younger women's concerns in relation to the risk of breast cancer with HRT

Informed reassurance is key to managing these concerns, which may already have been reinforced by less well-informed healthcare professionals (Box 1).

For women under 40 years of age, the baseline population risk of breast cancer is very low, and HRT in women with FH has not been found to increase the risk. Women with early menopause (40–45 years old) should likewise be advised that HRT before MAM is unlikely to increase the risk of breast cancer above that of an age-matched premenopausal woman, and thus the risk of breast cancer in relation to the years of HRT exposure in women with FH or early menopause should only be counted from MAM (i.e. 51 years).

Breast cancer risk calculators can be used to estimate the risk of breast cancer, factoring in any family history of breast cancer in first or second-degree relatives, and advice can also be sought from specialists in breast cancer genetics to inform individualised discussions and risk assessments. In fact, even for women carrying BRCA1/BRCA2 gene mutations (without a personal history of breast cancer), there is no evidence that HRT increases their breast cancer risk and thus HRT remains a perfectly reasonable option after prophylactic bilateral salpingo-oophorectomy.[96,168,169]

Although a recent meta-analysis reported that the use of HRT in postmenopausal women younger than 50 increased the risk of breast cancer diagnosis,[100] which contradicted previous evidence and advice, it suffered from two important caveats. First, the control group comprised of age-matched women who—by definition—had undergone an early menopause and thus would be expected to have a breast cancer risk below that of the average woman of the same age who was still menstruating. Second, the group of women under 50 years old included many who took HRT whilst still having natural cycles, and so their overall estradiol exposure was likely to have been above normal.

10.3 | HRT and risk factors for cardiovascular disease and stroke

Untreated POI and early menopause is associated with increased cardiovascular morbidity and mortality, attributed to the lack of estrogen, and it is presumed that the same risks apply to other forms of FH.[61,170] Meta-analysis suggests that HRT started before the age of 60 or within 10 years of the menopause in women without existing cardiovascular disease may result in reduction in atherosclerosis progression and coronary heart disease and has the potential to lower cardiovascular and all-cause mortality.[171] HRT is thus also likely to be cardioprotective in younger women with FH, due to its beneficial effects on cardiovascular risk factors including dyslipidaemia, insulin resistance, arterial compliance, endothelial function and blood pressure.[61,150]

Nevertheless, adverse cardiovascular outcomes were observed in 'secondary prevention' HRT trials that enrolled older women with established advanced atherosclerosis.[96] The 'timing hypothesis' proposes that, in the presence of established atheromatous disease in older postmenopausal women, the prothrombotic effect of estrogen may confer cardiovascular risk;[171] underpinning the adverse effects observed in trials of HRT in postmenopausal women, for example, in the Women's Health Initiative[172] and Heart and Estrogen/progestin Replacement Study (HERS) trials.[173] However, another confounding factor was that these studies used a particularly prothrombotic combination of estrogen (CEE, rather than native estradiol) and progestogen (medroxyprogesterone acetate).

HRT treatment of older postmenopausal women may also slightly increase the risk of ischaemic stroke and subarachnoid haemorrhage, with the greatest risk during the first year of use, but as previously discussed, the evidence quality is low and the data 'historic', mostly based on treatment of postmenopausal women with prothrombotic CEE+medroxyprogesterone acetate products.[174,175] Most younger women with FH, even those with CVD risk factors, have a low absolute risk of cardiovascular disease or stroke. Women previously treated with cranial radiotherapy are discussed in the 'late effects' section below.

Cardiovascular risk factors should be optimally managed, and women should be supported to address modifiable risk factors (obesity or smoking). Transdermal estradiol is often proposed to have a more favourable risk: benefit profile than oral estrogens, due to the effect on inflammatory markers, triglycerides, blood pressure,[176] as well as a lower VTE risk in women who may also be overweight or obese, but again most of the comparisons were with oral CEE or EE. More recent studies comparing transdermal with oral estradiol in

younger women have failed to show any significant differences in lipid profile, insulin sensitivity, C-reactive peptide (CRP) or blood pressure.[122,177] Progestogens with the least adverse impact on lipid metabolism, insulin sensitivity and blood pressure include oral micronised progesterone and dydrogesterone, transdermal norethisterone and intrauterine levornogestrel.[176] Some of the synthetic oral progestogens, such as medroxyprogesterone and norethisterone acetate, may attenuate the beneficial effects of estrogens on cardiovascular risk factors.[96] As discussed in Section 7, data relating to gender affirming hormone therapy and from the use of COC in obese women suggest that EE may have a specific adverse effect on cardiovascular risk factors and outcomes.[178–180]

There is no direct evidence base to guide decision making about HRT treatment in FH following a heart attack or stroke. Based on the HERS study findings,[181] HRT should be pragmatically paused for 6 months, followed by individualised reassessment of the potential risks and benefits of resumption, with a multi-disciplinary approach including shared decision-making with the patient and other relevant specialists. Such events may be atypical in younger women; other remediable risk factors should be optimised, and a thorough investigation of the aetiology of the event should be undertaken, (e.g. potentially including bubble-contrast echocardiography). Nevertheless, for most women under 45 years old, the expectation would be that HRT will be resumed, albeit potentially at a lower dose and using transdermal estradiol, with micronised progesterone, dydrogesterone, or intrauterine levonorgestrel.

10.4 | Migraine

Migraine with aura is a risk factor for ischaemic stroke in younger women (under 50 years), although the absolute risk of stroke remains very low. Migraine is not a contraindication to HRT use for women with POI (or other cause of FH).[168] Both over- and under-replacement with estrogens, and fluctuations in estradiol levels, have been reported to trigger migraine. For women with FH and migraine with aura, a transdermal estradiol-based HRT regimen is probably safer than COC, or CEE-based HRT and may also be safer than oral estradiol; providing steady levels without significant fluctuations may also be beneficial.[168]

10.5 | Previous venous thromboembolism (VTE) or risk factors for VTE

A detailed individual assessment is vital. For women with a previous VTE or a family history of VTE, it is important to understand whether the VTE was provoked or unprovoked, and whether there are persistent risk factors such as active malignancy, inherited thrombophilia, obesity, smoking, or immobility. It may be possible to address modifiable risk factors such as obesity and smoking. If the assessment raises concern or uncertainty, it may be helpful to request an assessment by a haematologist with a special interest in clotting disorders, to help inform shared decision making. Long-term or life-long anticoagulation may be recommended. Routine thrombophilia screening for women with no personal or family history of VTE is not recommended.

If resuming HRT is agreed, which would be the expectation in a woman under 45 years old, low-dose transdermal estradiol is recommended,[182] preferably with progestogen as IUS if combined HRT is required. The biological basis for this recommendation is that the hepatic first pass effect of oral estradiol may impair the balance between procoagulant and antithrombotic mechanisms, whilst transdermal estradiol has little effect on haemostatic factors. Again, CEE and EE-based COC are not recommended, as the evidence suggests they increase the risk of VTE;[107,180] no increased risk has been demonstrated with transdermal estradiol-based HRT.[183] Research data about the type of progestogen is less conclusive, but micronised progesterone and dydrogesterone do not seem to increase the VTE risk in post-menopausal women on HRT.[61,176,183] Although it seems likely that transdermal norethisterone is likewise neutral, there are no published data.

10.6 | Benign gynaecological conditions

Whilst both endometriosis and fibroids are hormone-sensitive, neither are contraindications to HRT for women with FH. Women with endometriosis who do not have a uterus should still initially be prescribed combined HRT, preferably in a continuous regimen, as estrogen alone may increase the risk of recurrence and possibly malignant transformation. If symptoms did recur or worsen, review and reassessment by their gynaecologist would be recommended.[168,184]

10.7 | Previous treatment and genetic risk factors for hormone-sensitive malignancies

10.7.1 | Breast cancer

A history of breast cancer should be considered a contraindication to systemic HRT. The risk of breast cancer recurrence with HRT is higher in women with estrogen receptor (ER) positive cancer, but women with ER-negative breast cancer are also considered to have an increased risk of recurrence with HRT, although this is beginning to be challenged for women with triple receptor-negative cancers (those negative for ER, progesterone [PR] and HER-2 receptors).[144] HRT may, in exceptional cases, be offered to women with severe symptoms of low estrogen when lifestyle modifications and nonhormonal treatment options are ineffective, but should only be done after detailed discussion with the woman and her breast-oncology team.

Unless vasomotor symptoms are having a particularly debilitating effect on quality of life and non-estrogen treatment options are ineffective, HRT is generally accepted to be contra-indicated in breast cancer survivors, whatever the ER status of the original tumour.[168]

Based entirely on precautionary principles, rather than any direct evidence of harm, vaginal estrogen is said to be contraindicated in

women with a history of breast cancer. However, as the systemic absorption is marginal[101] and no impact on breast cancer-specific mortality has been identified,[185] we consider this advice to be excessively cautious, particularly for women taking tamoxifen (rather than letrozole) or having ER-negative disease.

10.7.2 | Gynaecological malignancies

Cervical cancer is not hormonally responsive and there is thus no contraindication to HRT for women with FH who have been treated for squamous cell or adenocarcinoma of the cervix. Indeed, cHRT may even be advisable in women treated for cervical cancer with chemo-radiation (without hysterectomy).[186]

There are limited data about HRT in women previously treated for endometrial cancer, and discussion with their gynaecologist would be recommended: if they feel that the risk of recurrence is low, HRT for FH could be considered.[184]

For women previously treated for ovarian cancer, discussion with their gynaecologist/oncologist would be recommended, as HRT recommendations depend on the specific histological subtype.[184]

10.8 | Hepatic adenoma

There is an increased risk of hepatic adenoma associated with long-term use of EE-based COC, but this remains a very rare complication and no association with HRT is described.[187] In the event of incident hepatic adenoma arising in patient with FH taking HRT, a multi-disciplinary approach, with individualised case-by-case discussion with the hepatologist, would be recommended to agree a plan for treatment and surveillance, including shared decision-making about HRT given the paucity of relevant data.

10.9 | Obesity and alcohol excess

Obesity is a risk factor for VTE, cardiovascular disease and breast cancer, each of which has already been discussed. Alcohol excess is a risk factor for breast cancer, osteoporosis and fracture. Recommendations for HRT in women with FH and obesity include the use of transdermal estradiol and progestogens with lower VTE risk and a lesser impact on metabolic parameters (e.g. transdermal, micronised progesterone, dydrogesterone, or intrauterine levonorgestrel).[176] Supporting lifestyle modification, with referral to weight management/bariatric/alcohol-reduction services when indicated, should be part of routine care.

10.10 | Late effects of cancer treatment

Cranial radiotherapy (RT) is associated with an increased risk of developing a meningioma in the radiotherapy field. Although it is known that meningiomas may express PR and ER, it is not known whether HRT influences the risk of developing a meningioma in women previously treated with cranial RT in childhood. Given the benefits of HRT for FH and the lack of suitable alternatives, most late effects specialists would not view this as a contraindication to treatment. Routine MRI screening is not recommended, but there should be a low threshold for arranging imaging to investigate relevant symptoms in at-risk groups.[188]

For patients previously treated for a meningioma, or under surveillance with a meningioma, HRT should first be discussed with their neuro-oncology team and archived tissue should be immunostained for ER and PR to support informed decision making. Those whose tumours express PR might be best signposted to intrauterine rather than systemic progestogen as part of their HRT regimen.

Cranial RT in childhood is also associated with an increased risk of developing early cerebrovascular disease. The effect on this risk of HRT for FH is unknown. Most late effects specialists would follow the recommendations discussed above for those women having conventional stroke risk factors.

Women who were treated with radiotherapy to the chest (including total body irradiation, and upper abdominal radiotherapy) at a young age are at increased risk of developing breast cancer. There are guidelines about early breast cancer screening in this group.[189] High dose anthracyclines in the absence of chest radiotherapy also increases the risk of breast cancer, but there is inconsistent evidence to inform surveillance recommendations. Evidence to date does not suggest a significant risk of breast cancer attributable to HRT for POI in this patient group,[190] and most late effects specialists would not regard this as a contraindication, given the benefits of treatment and lack of suitable alternatives.

10.11 | Pituitary disease and hypopituitarism

Growth hormone (GH) plays a key role in regulating metabolic health and body composition, with major estrogen-mediated regulatory interactions between gonadal and the somatotrophic axes. Estrogen-based medications can therefore affect metabolic health though their effect on the GH axis. The effects of estrogen treatment are dependent on the form of estrogen, the route of administration and the serum concentrations achieved.[191]

All studies of oral estrogen treatment have shown lower concentrations of insulin-like growth factor-1 (IGF-1) associated with a compensatory rise in GH secretion. The inhibition of GH-mediated IGF-1 generation principally results from inhibition of hepatic GH receptor signalling, but also with greater secretion of estrogen-sensitive hepatic proteins, including those binding GH and IGF-1, which reduce bioavailability of both hormones. The effect on women with hypopituitarism on GH treatment is greatest with oral 20 μg EE, followed by 1.25 mg CEE and then 2 mg estradiol valerate,[192] and is negligible with transdermal estradiol at standard replacement doses.[193,194]

Therefore, women receiving GH treatment should ideally receive HRT based on transdermal estradiol. By contrast, younger women with active acromegaly (a profoundly appearance-altering condition)

may benefit from interim treatment with an EE-based COC as the preferred form of HRT pending the achievement of biochemical cure by standard means.[191]

11 | EFFECTS OF ESTROGEN DEFICIENCY ON BONE

Estrogen deficiency has marked detrimental effects on skeletal homeostasis. Women with untreated estrogen deficiency due to HA,[195–197] POI,[198] and CHH[199] all have significantly lower BMD, which can ultimately lead to fractures.[198,200–202]

Estrogen deficiency triggers osteoclastic activity and subsequent bone resorption through a number of pathways in humans, including through tumour necrosis factor-α (TNF-α),[203] interleukin-1β (IL-1β),[203] receptor activator of nuclear factor κB ligand (RANKL),[204] and sclerostin (Wnt signalling) pathways.[205] In addition, there may be further disturbances in upstream reproductive hormones.[32] This increase in bone resorption (and in some aetiologies a decrease in bone formation) can usually be detected clinically by changes in circulating bone turnover markers.[206]

In hypogonadal women of reproductive age, the detrimental acute and long-term effects on skeletal homeostasis may be even more profound than during normal menopause and so require prompt management.[207] We therefore recommend that all women of reproductive age experiencing hypogonadism for 6 months or more, have an assessment of BMD and identification of any additional risk factors for low bone mineral density.

11.1 | Bone recommendations in HA

At the more severe end of the spectrum, approaching AN, HA has additional detrimental effects on bone beyond estrogen deficiency (reviewed elsewhere[197]), with low concentrations of IGF-1,[208] androgens,[209] leptin,[210] and thyroid hormones,[211] and increased cortisol[212] contributing to the negative impact on skeletal homeostasis. These effects are demonstrated by the lower BMD observed in these women compared to those with normal-weight exercise-induced HA.[213] This highlights the need for a more complete management of women with HA, beyond merely estrogen replacement, to address psychological factors and promote nutritional factors.

Overall, the optimal treatment from a bone perspective in HA is recovery from the precipitating cause with restoration of menses. However, this is not always possible and thus pharmacological strategies are frequently required.

Regarding estrogen replacement, early transdermal physiological hormone replacement therapy[214,215] appears superior to COC in terms of surrogate markers of benefit to BMD, other structural bone parameters and bone turnover markers, albeit studies were relatively small[216,217] and contraception may also be an important consideration. This transdermal benefit is explained predominantly by that significant and unwanted IGF-1 suppression (in an already low IGF-1 state of HA) observed when estrogen (particularly EE) is delivered by the oral compared to transdermal route, as the latter avoids first-pass metabolism.[218] Other factors relating to the dose, duration and type of estrogen/progestogen exposure may also contribute to the benefits seen with transdermal replacement therapy compared to COCP.

Although, human interventional studies in women with AN have demonstrated small BMD benefits for 9 months of IGF-1 therapy (with COCP),[219] and 18 months of dehydroepiandrosterone (with COCP),[220] these treatments are not currently recommended or routinely available. Furthermore, low-dose transdermal testosterone replacement for 12 months does not appear to have a significant effect on BMD in women with AN (with or without amenorrhoea).[221]

Given the increased bone resorption observed in estrogen deficiency, it is tempting to consider typical anti-resorptive treatment with bisphosphonates. Although bisphosphonates have been shown to increase BMD in adult women with AN (with or without amenorrhoea),[221] their use carries a potential risk of neonatal complications and teratogenicity given their ability to cross the placenta and their long-lasting skeletal binding. Although recent human data are moderately reassuring in this regard,[222] we do not recommend their routine use in women who may become pregnant. The anabolic agent, teriparatide, has also been shown to increase BMD considerably after just 6 months of use in adult women with AN (with or without amenorrhoea), however there is a considerable risk that the bone benefits will be lost if the underlying AN persists after treatment is finished and so teriparatide is not routinely recommended.

11.2 | Bone recommendations in premature ovarian insufficiency

Similar to HA, POI carries an increased risk of low BMD and fractures.[198,223] However, the management of bone health in POI, presents a somewhat simpler challenge to HA where metabolic and additional factors frequently co-exist. In POI, we recommend early initiation of transdermal or oral physiological hormone replacement with consistent evidence supporting its superiority over the COCP.[126,224] This likely relates to the dose, duration and type of estrogen/progestogen exposure as well as lesser suppressive effects on IGF-1 (the latter in the case of the transdermal route). Replacement can typically be continued to the normal menopausal age or beyond depending on BMD and the presence of other estrogen-deficiency symptoms. Thereafter, bone management mirrors that in a woman who has reached the menopause at an expected age.

11.3 | Bone recommendations in CHH

Timely hormonal management of CHH before reaching adulthood is beyond the scope of these guidelines (reviewed elsewhere).[225] In adult CHH, estrogen replacement is essential for maintenance of

skeletal homeostasis.[199] As with HA and POI above, transdermal or oral physiological hormone replacement (rather than COCP)[224] is recommended as initial treatment from a bone perspective, when below normal menopausal age. Thereafter, bone management mirrors that in a woman who has reached the menopause at an expected age.

11.4 | Calcium and vitamin D recommendations

Alongside the above-targeted treatments to support bone health, for all the above conditions we recommend adequate dietary calcium intake (>700 mg/day, preferably from dietary sources, but otherwise supplemented)[226] and vitamin D intake (as dietary supplements or through safe sunshine exposure), sufficient to achieve a serum 25(OH)D concentration of at least 50 nmol/L and maintain normal range parathyroid hormone concentration.

11.5 | BMD monitoring recommendations

Depending on baseline BMD and clinical concerns (e.g. low baseline BMD, fracture history, additional bone risk factors, bone-specific treatments, compliance issues), we suggest repeat BMD testing by DEXA within 5 years of treatment initiation to reassess BMD to allow sufficient changes to be detected and guide subsequent frequency. Patients who had a normal BMD at baseline, without additional clinical concerns (such as those listed above), do not routinely require reassessment for another 5–10 years.

12 | FERTILITY

12.1 | The initial evaluation, including contraception

Not all women attending a Fertility clinic will be doing so for the reason of desiring pregnancy at that point; others having a known cause (or risk factor) for subfertility will be attending for general education in respect of their future options and, at this juncture, a discussion about contraception may be appropriate (see Contraception section in Primary care perspectives). The treatment of fertility issues in FH falls into two categories: ovulation induction for when the ovarian reserve is normal as it is in Central Hypogonadism, which might include ovulation induction or superovulation for in vitro fertilisation (IVF), and oocyte donation for when it is pathologically low, as in POI. The cause of hypogonadism is therefore an essential first consideration, not only to direct the nature of the fertility treatment required, but because there may be implications for pregnancy (e.g. cardiovascular safety in Turner syndrome) and/or the offspring (e.g. risk of them inheriting congenital HH).

12.2 | Preconception care

Preparation for pregnancy should focus on optimisation of any underlying medical conditions, including those that are the cause/effect of hypogonadism, or coexistent. It is also an opportunity to advise on any medication adjustments that might be required from a positive pregnancy test and in the first trimester, for example, increasing the dose of thyroxine replacement, or a plan for adjusting corticosteroid replacement should there be a first-trimester complication affecting maternal health such as hyperemesis.

In some conditions, pregnancy may have an impact on maternal heath, for example, the enlargement of a pituitary adenoma causing pressure symptoms, or increased risk of aortic dissection for a woman with congenital cardiac disease due to Turner syndrome, a potentially fatal event. Safe and successful pregnancy can be achieved by many women with Turner syndrome, following careful multidisciplinary preconception assessment and antenatal care.[42] Rarely, specialist pre-conception assessment may result in the recommendation that pregnancy should be avoided when the maternal risks are too high.

The prospective parent(s) should be counselled about what to expect in terms of any additions to routine antenatal care or foetal monitoring that might be required, any implications for labour or birth choices, as well as for postnatal and neonatal care.

When the cause of Central Hypogonadism is monogenic and the causative mutation is known, it is appropriate to consider pre-implantation genetic testing (PGT-M). This requires the creation of embryos by IVF (and a diagnosis-specific licence to test for the condition from the Human Fertilisation & Embryology Authority—HFEA). Foetal cell-free DNA can be isolated from maternal blood from the end of the first trimester[227] and used for noninvasive screening for monogenic disorders.[228] Chorionic villous sampling or amniocentesis are other options to obtain pregnancy samples for genetic testing, but these are invasive tests, and associated with a defined risk of miscarriage.

12.3 | Relevance of body mass index (BMI)

The chance of pregnancy and live birth is optimal for women whose BMI falls within the normal range for ethnicity. Women with low BMI (under 18.5 kg/m^2) should be encouraged to gain weight; even if this is not the underlying cause of their FH, the response to ovarian stimulation is better and pregnancy outcome becomes more favourable.[163] A BMI > 18.5 kg/m^2 is recommended in an international guideline on the management of HA.[163] However, lower BMI cut-offs should probably apply to women of South Asian origin.

High BMI alone is rarely a reason to advise against naturally-conceived pregnancy, although it might be a contributory reason to significant co-morbidities that could seriously affect maternal and/or foetal health. However, fertility treatment is not usually recommended when the BMI is greater than 35 kg/m^2, due to the associated anaesthetic and obstetric risks.[229] Currently in the UK,

BMI limits access to funding for IVF, although criteria may be slightly looser for ovulation induction, which is a medical, restorative treatment. Aside from funding issues, the decision to offer fertility treatment outside of the normal BMI range is a clinical one.

One of the challenges of achieving a healthy BMI from either end of the spectrum is that it takes time and yet fertility is a time-sensitive issue. The biggest predictor of live birth is the age of the woman when undergoing fertility treatment (or at oocyte collection for thawed embryo replacement or autologous oocyte thaw cycles) and, in the case of oocyte donation, the age of the donor at oocyte collection. It is therefore important that an individualised approach is taken when counselling the prospective parent on optimising BMI, and the risks versus benefits of delaying treatment to achieve this must be considered carefully. NHS-funded fertility policies in the UK have hard cut-offs regarding both age and BMI that will prevent access to treatment for some because of the time taken to achieve the necessary change in BMI. Others will simply be unable to achieve the required BMI without bariatric surgery or GLP1-agonist drugs. The implications of raised BMI for successful fertility treatment along with those for access to funding should ideally be discussed before fertility being actively desired.

12.4 | Specific considerations for women with POI

It is important to ensure that the karyotype of women with spontaneous POI is known before embarking on pregnancy, to identify those with Turner syndrome or Turner syndrome mosaicism, so that the appropriate pre-conception assessments, particularly cardiac, can be performed to reduce the maternal risks in pregnancy. Fragile X premutation should also be investigated due to the implications for relatives, especially for the potential offspring of a naturally conceived pregnancy, which is estimated to occur in up to 5% of women with POI.[61]

When POI is the result of chemotherapy with anthracyclines, or the heart has fallen within the field of radiotherapy to the chest, women should have a cardiac assessment and preconception counselling before embarking on pregnancy because of the small risk of cardiomyopathy and heart failure.[61]

The chance of pregnancy is reduced and the obstetric risks are increased after uterine irradiation, including total body irradiation. The adverse effects on uterine function are greatest when exposure occurs before puberty.[230] These women may achieve pregnancy, but then repeatedly miscarry or deliver prematurely due to uterine insufficiency.[61]

Finally, it is plausible that the chance of an embryo implanting following spontaneous ovulation may be higher if HRT is sequential rather than continuous.

12.5 | Fertility treatment for central hypogonadism (including HA)

The British Fertility Society and The National Institute for Health and Care Excellence (NICE) recommend ovulation induction (OI) as first line therapy for anovulatory women with functional hypogonadotropism.[231] A cycle of clomifene or letrozole ovulation induction may be indicated where there is thought to be some follicular activity and endogenous estrogen production (i.e. not for women with CHH, or hypopituitarism). There are, however, no data on what might be the serum estradiol threshold below which oral OI is ineffective. Otherwise all three guidelines recommend pulsatile GnRH for its low risk of multiple pregnancy (except in hypopituitarism). However, there is no longer a commercially available product in the UK. Instead, GnOI is recommended using FSH products with luteinising hormone (LH) activity (e.g. as hCG) delivered as a daily subcutaneous dose. GnOI has a risk of multiple pregnancy, which can be minimised to 5% by careful use of a low dose, step-up regimen, preferably starting with doses below 75 IU each cycle, in conjunction with a strict cancellation policy when there are three or more follicles with diameter greater than 15 mm developing.[232] However, even with cautious dose escalation this leads to a high number of cancelled cycles: 25% of women with CH starting a cycle in the series of White et al. Most pregnancies occur in the first three cycles of treatment.[232,233]

GnOI can be offered to women with hypogonadism who are of reproductive age and have infertility due to anovulation, provided they do not have elevated FSH; although in some, FSH will not rise, no matter how low the number of oocytes remaining in the ovary. Other markers of ovarian reserve are unreliable in CH, including anti-mullerian hormone (AMH), inhibin B, antral follicle count and ovarian volume. Sometimes, GnOI will unmask coincidental POI with no ovarian follicular response despite high doses of FSH. Clinicians should be prepared to use higher doses of gonadotropins for women with CH than with PCOS, although a cautious approach with a strict cancellation policy is still needed; 300 IU/day is the suggested maximum dose.[232]

Neither the BFS nor NICE make a recommendation for the number of GnOI cycles to offer, but given that most pregnancies occur within the first three and few after more than six cycles, somewhere between three and six cycles would be reasonable, depending on local resources and individual preference. GnOI is a demanding treatment, requiring twice weekly transvaginal ultrasound scans to monitor follicular development. This takes a median of 30 days in HH, and longer still in those with severe gonadotropin deficiency.[232] For heterosexual couples having vaginal intercourse, clinic direction on when (and when not) to have intercourse can lead to sexual dysfunction and reduced episodes of intercourse. If donor sperm is required, the associated costs may also limit the number of cycles offered or accepted.

Comparing live birth rates with GnOI by cause of anovulation does not reveal any differences and rates are the same as in natural cycles.[233] In a similar series from a different centre which reported similar pregnancy rates, there was no relationship between endometrial thickness and pregnancy rate.[232] Endometrial thickness was less on the day of hCG trigger in cycles that resulted in pregnancy in those with HH compared to those with PCOS.

However, reported miscarriage rates are consistently higher in those with congenital HH compared to those with PCOS, which could

reflect reduced uterine function or size.[232,233] In the series of Balen et al., the highest miscarriage rates were in those with HA, the majority of whom would be expected to have undergone normal puberty, but for whom prescription of HRT may be inconsistent.[233] There are other explanations for the higher miscarriage rate in hypogonadotrophic women, including poor function of the corpus luteum, for which luteal support with progesterone or hCG is generally recommended.[65]

Meanwhile, recombinant leptin and Kp analogues are being researched as potential novel treatments to achieve fertility in HA.[234] Kp administration increases levels of GnRH/LH pulsatility in women with HA,[235,236] and may have direct positive effects on bone metabolism.[237] Although studies have demonstrated that recombinant leptin can restore ovulation in some women with HA,[238] the costs of therapy are prohibitive and far exceed those GnOI.

IVF can be offered successfully to women with CH (including HA) when their conception delay is multifactorial (e.g., with coexistent male or pelvic factor) or if ongoing pregnancy has not been achieved after a course of GnOI cycles. When multiple pregnancy rates with IVF were high before the introduction of elective single embryo transfer policies, this was one of the strong arguments in favour of ovulation induction. Another reason was the lower risk of ovarian hyperstimulation syndrome (OHSS) with GnOI compared to that with IVF.[232,233] Now that embryos can be successfully stored, the risk of OHSS in IVF cycles can be managed by storing all resultant embryos instead of transferring one, with a later thawed embryo transfer cycle. The protocol with lowest risk of OHSS in an oocyte collection cycle (i.e. using a surge of endogenous LH in response to a bolus dose of a GnRH agonist to stimulate oocyte maturation instead of administering hCG) cannot be used reliably in this population.

Both these advances are possible because of the success of using stored embryos, which raises the question about whether GnOI or IVF is the more cost effective in this group, given that most couples and individuals want more than one child and many will create more embryos than are needed for one live birth.[239] However, IVF success is related to the number of oocytes collected and the number of embryos available for transfer. Severe gonadotropin deficiency, requiring higher dose and longer stimulation for follicle development, may compromise the number of oocytes collected and the potential for there to be stored embryos for subsequent pregnancies.

12.6 | Fertility treatment for POI

Oocyte donation is the only proven treatment in POI of all causes, including Turner syndrome.[168,240] Live birth rates are similar to those for women undergoing own egg IVF for conception delay, matched to the age of the donors, which is usually under 35 years. Oocyte recipient pregnancies appear to be at slightly higher risk of obstetric complications than autologous oocyte pregnancies.[168]

Altruistic egg-donors broadly fall into two categories in the UK, whether known to the recipient or anonymous. The typical 'known' donor would be a sister or close female friend, who had already completed their family and had received appropriate counselling. Anonymous donors are members of the general public, or occasionally women having superovulation-IVF with an excellent predicted response in terms of the number of oocytes retrieved, but who need to self-fund their treatment and who agree to donate approximately half their recovered oocytes: they are generally known as 'egg sharers'. In this situation, a fertility clinic may agree a more favourable tariff. It is important to recognise that such donation is only initially anonymous: children can find out about their donor from the HFEA at the age of 18.

There are no proven fertility treatments using the woman's own oocytes,[241] despite women with POI retaining some ovarian follicles at least for a while after onset of the clinical condition. Evidence of ovarian activity will be found in 25% of women with POI after onset.[60] Although a small randomised controlled trial found an increased ovulation rate with estrogen pretreatment before GnOI,[242] prescribing estradiol up to the point of GnOI would be standard of care anyway for all forms of FH.

Where available, in vitro maturation (IVM) of oocytes is an experimental option for pregnancy for the small group of women with autoimmune POI but yet a relatively normal number of antral follicles.[243] These are often described as resistant ovaries, as gonadotropin levels are high and ovarian stimulation is unsuccessful. A range of other experimental therapies have been proposed to increase oocyte yield, including injection of platelet-rich plasma in the ovary and infusion of bone-marrow-derived stem cells. These treatments remain either in their infancy, or subject only to poorly controlled trials with thus no clear evidence of benefit.[244,245]

Other than oocyte donation, probably the most important fertility intervention that can be offered to women with POI desiring pregnancy is HRT (which is not contraceptive) and encouragement to have intercourse frequently and regularly. Realistic expectations of pregnancy must be given, including that most natural pregnancies in POI occur within the first year of diagnosis.[60]

No guidelines exist about offering fertility investigations where POI has been previously diagnosed. Assuming a male partner, it would be reasonable to perform a semen analysis if natural conception is being attempted. Although waiting for 1 year of regular unprotected intercourse is recommended,[229] it seems inappropriate in women with POI given the extremely low chance of natural conception. Tests of tubal patency carry a small risk of pelvic infection, as do surgical procedures to optimise the pelvic anatomy if abnormal, and therefore probably cannot be justified for such a small potential pregnancy rate. There may be benefits from tubal flushing, given that the number of natural pregnancies conceived in few months afterward in the general fertility population is slightly increased.[246] The potential for this to be developed as a fertility treatment has been raised by an RCT demonstrating an increase in natural conceptions with an oil-based contrast medium rather than a water-based one.[247] This has not been validated in the POI population and is currently being investigated further in an international multicentre RCT.

12.7 | Optimising the endometrium

Exogenous estradiol in higher doses than for standard HRT is used in oocyte recipient cycles to thicken the endometrium in preparation for embryo transfer. Although the dose of estradiol positively correlated with implantation and pregnancy rates, it did so only indirectly via an effect on endometrial thickness in a series of 68 oocyte-recipient cycles in 29 women with TS. Dose or duration of estradiol did not influence these outcomes once the threshold endometrial thickness was reached (identified in this series as 6.5 mm).[248] A retrospective analysis of over 4000 oocyte recipient cycles (for all indications) similarly indicated that endometrial thickness above threshold (identified as 5 mm) did not influence implantation, pregnancy or miscarriage rates.[249] The duration of exposure to estradiol may be important to endometrial development and function, as well as the dose. It is notable that subsequent cycles were more successful than initial cycles for women with Turner syndrome, which the authors attributed to experience of the first cycle allowing protocol modification in the second to achieve a thicker endometrium.[248] There may also have been a priming effect of the first cycle. Live birth rates were not analysed by estradiol replacement protocol or dose in either study and later pregnancy complications were not included.

12.8 | Fertility preservation

Fertility preservation (the storage of mature oocytes, embryos or ovarian tissue for future pregnancy) is not an option for women with established POI as their ovarian reserve has already fallen below a critical point. However, there is a role for oocyte cryopreservation for women at risk of POI because of required medical or surgical intervention.[240,250] Most women at risk of spontaneous POI are not identified soon enough for this to be an option. It can be considered in women still with sufficient ovarian function after diagnosis of a genetic risk, for example, Turner syndrome, carriage of the fragile X premutation or possibly a strong family history of POI. There is considerable uncertainty about the value of ovarian tissue cryopreservation when the POI is due to a primary ovarian disorder (rather than iatrogenic) such as TS.[251]

There are no validated tests to predict when the reduction in ovarian reserve will become clinically significant in an at-risk population, and many women will anyway have completed their families by the time of onset. The potential role of AMH in this regard has recently been reviewed,[57] confirming the lack of good data and the uncertainties involved. National programmes for genome-wide screening are already being established in some countries, including the UK and France, and it is hoped that this will help to identify the multiple genetic factors collectively responsible for POI as well as monogenic ones. Notwithstanding cautions about predicting onset of critically reduced ovarian reserve/POI, the future yet could hold a screening test for POI, given that there is a successful intervention in the form of fertility preservation whilst the ovarian reserve is sufficient.

12.9 | Uterine volume in FH and its potential significance

Earlier estrogen replacement during pubertal induction is associated with increased uterine size in adults and concomitant growth hormone deficiency is associated with smaller size.[252] There have been no studies investigating whether pubertal induction regimens affect future pregnancy outcome.

Congenital FH is associated with significantly smaller uterine size in adult life than in matched nulliparous women, despite ongoing HRT in standard doses.[253] The reasons for this are uncertain, but could include delayed diagnosis and late initiation of estrogen treatment, shortcomings of historic regimens for pubertal induction,[11,12] or simply that even the higher end of standard dose HRT formulated for postmenopausal women may not be adequate for younger women with FH.[148] Small uterine size could be a determinant or a marker of poor uterine function, as increased risk of miscarriage, caesarean birth and foetal growth restriction have been described in association with different causes of hypogonadism.[248,254,255] Burt et al. identified a positive correlation between serum estradiol and uterine volume in women taking 17β-estradiol HRT, indicating that current dose of estradiol might influence uterine volume.[253] It is not known if optimising estrogen replacement for uterine size before fertility treatment in hypogonadism improves pregnancy outcomes.

In summary, although the smaller uterine volumes observed in women with congenital hypogonadism who required pubertal induction are concerning, evidence that this impacts on actual fertility outcomes remains elusive. Although miscarriage rates could be related to this, other issues could be causative. Nevertheless, women with hypogonadism should be advised that pregnancy following fertility treatment may be at increased risk of complications, and those who are not taking HRT before commencing fertility treatment should be encouraged to do so for as long as possible beforehand. This information may be particularly important for women with HA, who are not always prescribed HRT in the hope that lifestyle change of itself might be implemented and eventually prove successful.[163] Protocols for pubertal induction in congenital FH should be optimised for future pregnancy and live birth, and including sonographic monitoring of uterine dimensions, with further research needed in this area.[11]

12.10 | Antenatal and postnatal care

For FH women with TS, hypopituitarism, or other significant medical issues, joint antenatal care should be provided by appropriately experienced endocrinologists, obstetricians and midwives, ideally in the setting of a multidisciplinary maternal medicine antenatal clinic with access to relevant specialist services. Some obstetric services include an obstetric physician. The maternal team is usually best placed to provide information to the prospective parent(s) about pregnancy and childbirth, although the exact set up of services locally will dictate the appropriate referral route for a preconception

discussion before commencing fertility treatment. Moreover, routine recommendations for pregnancy and breastfeeding should not be overlooked.

Women who are exclusively breastfeeding and amenorrhoeic have circulating estradiol levels in the range of 70 to 200 mol/L range (Section 4.4) and progesterone concentrations under 3 nmol/L. Lactation is thus a state of physiologically absent progesterone secretion and relative hypoestrogenaemia, and so full-dose HRT with progestogen should ideally not be resumed until completion of exclusive breast-feeding. Specifically, it is not recommended that a reproductively 'normal' woman resumes COC whilst breastfeeding due to evidence of impaired milk secretion. Nevertheless, in practice, some women with profound hypogonadism and severe estrogen deficiency do experience difficulty breastfeeding and transdermal estradiol (up to 200 mcg patches) as monotherapy is, in practice, not deleterious to breastfeeding outcomes, including infant growth and sex hormone profiles.[256] Thus, the protocol in some units is to prescribe low-dose estrogen-only HRT (0.5 mg oral or 25 mcg patches) for the duration. Finally, for women choosing the breastfeed for more than a year or two, an informed discussion should be had about reintroducing full-dose HRT, particularly in the context of established osteopenia or osteoporosis.

Women with CHH who achieve biological parenthood may transmit the condition to their offspring at a rate of perhaps 5%–10% and this necessarily forms part of pretreatment counselling. Moreover, there is a unique window of opportunity in the first 4–8 postnatal weeks to diagnose (or exclude) CHH in the infants by measuring the reproductive hormones associated with normal minipuberty.[257–259]

13 | PRIMARY CARE PERSPECTIVES ON FH

Some patients will be managed entirely in primary care, but even for patients under secondary care, their primary care physician can contribute very usefully beyond just providing timely repeat prescriptions for HRT.

13.1 | Management and monitoring in primary care

Optimisation of lifestyle factors is key to reduce the long-term health risks which include cardiovascular disease, diabetes and osteopenia/osteoporosis. Primary care teams are in a key position to facilitate this aspect of management. Aspects to consider include ensuring a healthy diet and maintaining a normal body weight; regular weight-bearing exercise; smoking avoidance/cessation; alcohol minimisation; calcium and vitamin D optimisation, and assessing blood pressure, weight and smoking status annually.

There is a shared responsibility between primary care and the relevant specialties, whether endocrinology, paediatrics or gynaecology to determine their respective roles in monitoring various aspects of treatment. Optimisation and monitoring of HRT doses and BMD assessments lie within secondary care, but primary care has a key role in advising about contraception and sexual health and in providing ongoing annual review, prescribing, and other lifestyle advice.

HRT for women with FH needs to be among their long-term repeat prescriptions, rather than just being 'on demand', although patients continue to encounter obstables in this respect. Moreover, although some practices recall patients for quarterly blood pressure monitoring, due to understandable confusion of HRT in FH with COC or menopausal HRT, this is not required for women with FH on estradiol-based HRT.

13.2 | Sexual function and contraception

Sexual dysfunction is common in women with FH and is frequently under-reported. Primary care physicians and specialists involved in the care of these patients should specifically enquire about these issues as part of normal care. In addition to systemic HRT, local (vaginal) estrogen therapy helps to manage both vaginal dryness and urinary symptoms, and its wider use should be actively encouraged. As with postmenopausal women, loss of libido is another common concern (and again under-reported), and the use of testosterone therapy can prove beneficial in some cases, but usually only after biochemical optimisation of estrogen replacement.[168]

Contraception is most often requested, prescribed and monitored within primary care, and contraceptive requirements for women with FH vary significantly according to the cause. Some women have a negligible chance (or risk, according to perspective) of conceiving naturally and therefore do not require contraception, comprising those with CHH, CPHD; acquired organic hypopituitarism due to tumour or treatment thereof, or POI/gonadal dysgenesis with absent puberty at diagnosis. Those with the greatest chance of conceiving naturally are women with hyperprolactinaemic CH, who may resume ovulating within weeks of commencing dopamine-agonist treatment, and those with HA, whose condition may remit completely with lifestyle change. Therefore, although most of these women will require fertility treatment to achieve pregnancy, contraception should nevertheless form part of the initial discussion unless fertility is desired at the outset.

There is also a small but definite chance of ovulation in 46XX POI of postpubertal onset, especially in the early years after diagnosis, and contraception should be used in the event that pregnancy would not be welcome at that point. This can be a particularly difficult discussion for these women, as they need to balance their very low lifetime chance of conceiving a biological child with the consequences of an unplanned pregnancy that might be devastating according to personal circumstances. Younger women who developed POI following chemotherapy for childhood cancer may experience recovery of ovarian function, depending on the intensity and composition of the treatment regimen, and should also be counselled about contraception until their final ovarian function (or lack of it) has definitively been established.

Although (as per Section 9) we recommend 17β-estradiol-based HRT for women with FH, it is not contraceptive unless combined with a levonorgestrel intrauterine system (IUS) or long-acting systemic progestogen, or careful use of barrier methods. Therefore, the patient may instead prefer to use a COC as a direct alternative to HRT, in which case we advise a 17β-estradiol-based product in line with our recommendations in relation to HRT.

14 | CONCLUSIONS

FH comprises a disparate group of conditions affecting younger women, many of whom have other significant medical issues and/or may need to continue taking HRT for several decades. Despite this, no HRT products have been specifically tailored for women with FH. FH is often confused with menopause; women with FH frequently describe obstacles in accessing HRT, including overstated warnings about breast cancer and cardiovascular risks, which can lead to prolonged gaps in treatment or premature discontinuation. Instead, the benefits of physiological estradiol replacement should be emphasised, which confer no risks above the baseline for eugonadal females. Biological parenthood has long been achievable for women with CH through ovulation induction or IVF, but many patients assume that they are irrevocably infertile and thus may not seek help unless prompted to do so. Management of FH may be modified by the underlying aetiology and so specialist advice is usually necessary to establish a treatment plan. Future research is needed to establish the monitoring and management requirements to optimise health outcomes for women with FH.

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