Received: 24 June 2018 | Revised: 18 August 2018 | Accepted: 5 September 2018

DOI: 10.1111/cen.13850

CLINICAL QUESTION

WILEY

Fertility induction in hypogonadotropic hypogonadal men

Matthew Prior[1] | Jane Stewart[1] | Kevin McEleny[1] | Andrew A. Dwyer[2] | Richard Quinton[3,4]

[1]Newcastle Fertility Centre at LIFE, Newcastle-upon-Tyne Hospitals, Newcastle upon Tyne, UK

[2]William F. Connell School of Nursing, Boston College, Chestnut Hill, Boston, Massachusetts

[3]Institute of Genetic Medicine, University of Newcastle-upon-Tyne, Newcastle upon Tyne, UK

[4]Department of Endocrinology, Newcastle-upon-Tyne Hospitals, Newcastle upon Tyne, UK

Correspondence
Matthew Prior, Newcastle Fertility Centre at LIFE, Newcastle-upon-Tyne Hospitals, Newcastle upon Tyne, UK.
Email: Matthew.Prior@nuth.nhs.uk

Summary

Men with hypogonadotropic hypogonadism (HH) are typically azoospermic, and yet HH is one of the few treatable forms of male infertility. Sperm induction protocols using gonadotrophins aim to replicate the natural endocrine control of spermatogenesis. Previously virilised men with adult-onset HH and normal testicular volume respond well to monotherapy in which human chorionic gonadotrophin (hCG) acts as a long-acting LH-analogue stimulating spermatogenesis. However, this approach is rarely successful for men with congenital HH (CHH) (eg, Kallmann syndrome), for whom combined gonadotrophin therapy (hCG + follicle-stimulating hormone [FSH]) is an absolute requirement to maximise fertility potential. Key baseline predictors of successful spermatogenesis-induction include prior spontaneous testicular development (ie, testicular volume [TV] > 4 mL), serum inhibin B (I_B) concentration >60 pg/mL and no history of maldescended testes (cryptorchidism).

KEYWORDS

fertility, hypogonadotropic hypogonadism, spermatogenesis

1 | INTRODUCTION

Historically, fertility induction regimes involved an initial phase of human chorionic gonadotrophin (hCG) monotherapy to normalise serum testosterone (T) concentrations prior to the introduction of follicle-stimulating hormone (FSH). However, for those men lacking testicular development (TV ≤ 4 mL) this approach is not grounded in the ontogeny of testicular maturation. Seminal studies demonstrate nocturnal, sleep-entrained GnRH pulses stimulate FSH secretion (and hence, an increase in TV is the first sign of pubertal onset) long before LH-induced serum T concentration rises into the adult normal range.[1] Accordingly, men with severe CHH, as demonstrated by prepubertal testes (≤4 mL) and/or a history of cryptorchidism, may achieve better results with a more physiologic based approach to drive Sertoli and germ cell proliferation (and testicular growth). This can be achieved using a sequential approach with FSH pre-treatment prior to adding hCG.[2] Even with optimised regimens, few men with CHH achieve entirely normal semen parameters by WHO criteria, but fortunately, this does not preclude natural conception.[3]

Regardless of the approach, sperm induction is best performed in a multidisciplinary context with concomitant evaluation of the female partner, to maximise the chance of live birth and allow timely deployment of assisted reproduction treatments (ART) when natural conception does not occur. In the context of CHH, pre-treatment genetic counselling is advisable before fertility treatment due to possible risk of transmission to children.[4]

In this case-based review, we describe the fertility-inducing regimens and treatment outcomes of two couples, both of which comprised a man with HH. The male partner in Case 1, had a good prognosis at baseline, evidenced by proven fertility prior to the onset of HH in adult life. The patient in Case 2 had the most severe form of CHH, evidenced the history of cryptorchism, small prepubertal testes and failure to initiate spontaneous puberty. Nevertheless, both couples ultimately became biological parents, albeit with some differences in how they achieved this.

2 | CASE 1

A 30-year-old man was followed in the endocrinology clinic after transphenoidal decompression of cystic pituitary adenoma 3-years previously. He was taking levothyroxine 150 μg and a sachet of

testosterone transdermal gel (Testogel® 5 g) daily for thyrotroph and gonadotroph deficiencies, respectively. He had proven fertility having fathered two children with his former wife and his new partner now desired to conceive. Baseline investigations off testosterone gel for 2 weeks revealed HH (LH 1.2 [1.8-12.0 IU/L]; FSH 2.2 [1.3-19.3 IU/L]; T 1.2 [9-25 nmol/L]) and azoospermia. Clinical examination showed he was well-virilised with a TV of 12 mL, body mass index was 28.6 kg/m^2, waist circumference 102 cm and normal blood pressure. His current partner aged 24 years had regular ovulatory cycles, no history suggestive of other fertility issues and a normal pelvic ultrasound scan.

He commenced self-administered subcutaneous injections of hCG (1500 IU twice weekly) achieving normal serum T, oestradiol (E_2) and haemoglobin (Hb) concentrations and increased TV (from 12 to 14 mL) within 3 months. After 7-months of treatment, repeat seminal fluid analysis showed oligozoospermia (5×10^6/mL [WHO reference: >15×10^6/mL]). Sperm count rose to 30×10^6/mL at 11 months and 51.5×10^6/mL at 14 months, at which point his partner was already 14 weeks pregnant. The partner subsequently delivered a healthy baby girl at term. At this point, the primary care organisation recommended he discontinue hCG prescribed by his general practitioner (GP), as it was considered to be a "red drug" restricted to secondary care prescribing. However, with specialist support, the GP agreed to continue hCG treatment as it was less expensive than his previous testosterone replacement product. Two years later, the partner delivered a healthy baby boy at term. The couple then considered their family to be completed and our patient reverted to direct testosterone replacement.

3 | CASE 2: CONGENITAL HH

A 23-year male presented for fertility consultation after a year of trying to conceive with his girlfriend, who was 21 years old, with regular ovulatory cycles and a history of termination of pregnancy in a previous relationship. He had been born with bilateral cryptorchidism that was surgically corrected at 4 years of age. He did not spontaneously begin puberty and commenced Sustanon® injections at 17 years to induce secondary sexual characteristics, initially 100 mg monthly, increasing to 250 mg every 2-3 weeks. Based on a single seminal fluid analysis showing azoospermia, the patient's GP told him that he would be never be able to have children.

Examination showed prepubertal scrotal testes (TV 3 mL bilaterally). Hormonal profiling off testosterone injections for 4 weeks revealed severe HH with undetectable serum gonadotrophins (LH < 0.5 IU/L, FSH < 0.4 IU/L) and I_B (<15 [80-325 pg/mL]), with frankly hypogonadal serum T (0.6 nmol/L). MRI of the hypothalamo-pituitary region was unremarkable, and he had otherwise normal anterior pituitary function. On questioning, he reported an absent sense of smell, findings consistent with the diagnosis of Kallmann syndrome (KS). The couple were counselled about the small but defined risk of children inheriting KS but were unequivocal in their desire to proceed.

Pre-treatment with FSH (human Menopausal Gonadotrophin [hMG] 75 IU daily by subcutaneous self-injection) was initiated, achieving a physiological serum FSH concentration of 5-6 IU/L. After 2 months of pre-treatment, TV increased to 4 mL, I_B rose to 85 pg/mL, and hCG 1500 IU three times a week by subcutaneous injection was added. With the addition of hCG, serum T and haemoglobin concentrations normalised and I_B plateaued at 95 pg/mL. There were no supraphysiological excursions in his serum oestradiol (that would otherwise have necessitated a reduction in hCG dose in order to avoid the risk of gynaecomastia). Over the following 12 months, TV progressively increased to 8 mL. At 18 months, seminal fluid analysis showed a sperm count of 1×10^6/mL.

Rather than waiting to see if more prolonged treatment might achieve a higher count, the couple elected to proceed straight to assisted reproduction (ART). His partner underwent controlled ovarian stimulation, oocyte retrieval and intracytoplasmic sperm injection (ICSI), achieving four embryos. The first single embryo transfer was unsuccessful, but they conceived after a frozen embryo transfer. She gave birth to a healthy baby boy at term with no clinical signs of Kallmann syndrome (ie, cryptorchidism or micropenis). One embryo remained frozen for future embryo transfer, and sperm was cryopreserved before reverting from gonadotrophin to testosterone treatment.

4 | HYPOGONADOTROPIC HYPOGONADISM

Hypogonadotropic hypogonadism is the only cause of male infertility that can be successfully treated with gonadotrophin replacement therapy. CHH and congenital combined pituitary hormone deficiency (CPHD) are rare diseases, affecting around 1-in-4000 and 1-in-10 000 males, respectively. However, acquired HH is much more common and may result as a sequela of treatment for intra- and parasellar tumours, but also from iron overload (haemochromatosis), chronic opiate use and inappropriate androgen use.

Although men with HH are all typically azoospermic, predicted response to therapy falls into three broad groups based upon their baseline characteristics. At the mildest end of the spectrum—and having the most favourable outcomes—are men with adult-onset HH who had fathered children prior to the onset of HH, as illustrated by Case 1. At the opposite end of the spectrum—and having the least favourable outcomes—are men with severe CHH (or CPHD), with small testes (TV ≤ 4 mL) and history of bilateral cryptorchidism, as illustrated by Case 2. Approximately one-third of CHH patients exhibit a milder phenotype, evidenced some degree of spontaneous puberty at presentation—typically arrested early puberty, rather than complete failure of pubertal onset—and these men with TV > 4 mL and no history of cryptorchidism have a prognosis for spermatogenesis-induction that falls somewhere between the clinical extremes illustrated by Cases 1 and 2.[5]

5 | ENDOCRINE CONTROL OF SPERMATOGENESIS

Spermatogenesis requires the coordinated action of FSH and endogenous testosterone. Puberty is initiated by GnRH-induced pulsatile LH

secretion, with low-frequency, nocturnal pulses initially favouring FSH secretion over LH.[1] Serum LH, FSH and testosterone concentrations increase progressively and extend into the waking hours, culminating in reproductive maturity. Notably, LH and FSH have a differential effect on the testes. LH stimulates maturation of the interstitial Leydig cells that secrete T. FSH acts on the seminiferous tubules to induce and maintain spermatogenesis. In early puberty, FSH stimulates the proliferation of immature Sertoli cells that is essential for seminiferous tubular development.[5] The seminiferous tubules account for approximately 90% of TV; hence, the size of the testes is a critical indicator of fertility potential. Importantly, both FSH and T are necessary for both quantitatively and qualitatively normal spermatogenesis.[6]

5.1 | Testicular development: minipuberty and puberty

The hypothalamic-pituitary-gonadal (HPG) axis is active during the third trimester of foetal life but is subsequently suppressed towards term due to the negative feedback of placental hCG. This restraint is removed at birth, leading to a reactivation of the axis during the first 6 months of life, peaking around 2 months postnatally.[7] During this so called "mini-puberty", gonadotrophins and testosterone concentrations can approach adult levels. Importantly however, Sertoli cells do not express the androgen receptor until age 5 years, so despite the high intra-testicular T concentration during mini-puberty, the testes do not mature and spermatogenesis is not initiated. Thus, the early neonatal period is a key proliferative window for germ cells and immature Sertoli cells.

Several serum markers provide insights into testicular development. Inhibin B is secreted by mature Sertoli cells and is an important regulator of FSH in adults.[8] Serum concentrations can provide a proxy for the Sertoli cell population in the testes—thus, very low inhibin B concentrations are a negative predictor of spermatogenesis.[9] Antimullerian hormone (AMH) is secreted by immature Sertoli cells and is down-regulated by T. As such, it is highest in early puberty and decreases with rising serum T concentration.

In early puberty, FSH concentrations rise with low-frequency, sleep-entrained GnRH secretion,[1] resulting in a wave of Sertoli cell proliferation that has direct consequences on TV and fertility. As puberty progresses, LH-induced T secretion from the Leydig cells increases intra-testicular T concentrations that promote cell maturation and ends the proliferative phase. Intra-testicular "paracrine" testosterone is around 30-times higher than serum "endocrine" concentrations,[10] and these high concentrations are an absolute requisite for spermatogenesis. In parallel, the seminiferous cords develop a lumen marking transition to tubules.

6 | FERTILITY INDUCTION WITH GONADOTROPHINS IN MEN

A logical approach to fertility induction in men with HH is to replace GnRH in a pulsatile manner via an infusion pump. Protocols aim to mimic normal physiology by delivering doses in a pulsatile manner. GnRH dose is titrated to induce serum T levels in the adult range and spermatogenesis. Dose frequency is typically two hours and dose required to achieve normal serum T levels varies widely (25-600 ng/kg).[5,9] The time to reach normal serum T level largely depends on baseline testicular volume. Studies show normal adult T levels can be reached in as little as 1 week and over 90% of patients normalise T by 6 months.[9,11-13] The largest study found sperm was present in 24/31 after 12 months and 42/51 by 24 months. Median sperm counts were in the normal range (WHO reference: >15 × 10^6/mL) for men who had undergone partial or complete puberty but also sufficient for ICSI treatment in men with absent puberty.[9] Currently, this modality is delivered only in some research settings as wide use is limited by the availability of drug and/or suitable infusion device capable of delivering pulsatile GnRH, as well as the clinical expertise required to titrate and monitor pulsatile GnRH therapy. Moreover, this approach is not effective for patients with primary pituitary disease. Importantly, fertility outcomes are similar between pulsatile GnRH and gonadotrophin regimens.[14] Thus, gonadotrophin treatment is the most common approach to fertility induction in men with HH.

6.1 | Human chorionic gonadotrophin (hCG) monotherapy

Men who acquire adult-onset HH following full pubertal development have a form of infertility that is readily amenable to hormonal treatment. Serving as a long-acting LH-analogue, hCG given by self-administered subcutaneous injection 2-3 times per week, induces testicular development and spermatogenesis.[15-17] Fertility is typically achieved within 3-9 months.[2] If sperm are not observed in the ejaculate, or the count remains suboptimal (without conception), FSH should be added to the regimen (ie, 75-300 IU, 3 times per week).

Importantly, hCG monotherapy is only viable for those HH men at the mildest end of the spectrum, with partial (ie, TV ≥ 4 mL) to normal testicular development. Of those men with a TV < 4 mL, fewer than half will ever develop sperm in their ejaculate—even with prolonged hCG monotherapy for up to a decade.[2] Semen analysis parameters rarely normalise by World Health Organisation criteria,[18] although suboptimal sperm counts do not necessarily preclude fertility in men with HH.[3]

6.2 | Combined gonadotrophin therapy: FSH and hCG

Men with the most severe HH exhibit prepubertal testes (TV < 4 mL) and have the poorest outcomes for sperm induction treatment. Combined gonadotrophin therapy (hCG + FSH) has been the standard for inducing fertility in men with CHH. Notably, regulatory requirements for licensing new (recombinant or long-acting) FSH products has traditionally required subjects to remain azoospermic after a phase of hCG monotherapy (prior to receiving the investigational

drug) as part of combined hCG + FSH therapy. However, this approach is not grounded in developmental physiology.

Follicle-stimulating hormone preparations, in the form of highly-purified urinary gonadotrophins (hMG), recombinant FSH (rFSH), or long-acting analogue are given by subcutaneous self-injection (75-300 IU) three times per week, with the intended goal of achieving serum FSH concentration in the range of 4-8 IU/L. Time to develop sperm in the ejaculate ranges from 3 to 19 months, with median times in the 9-12 month range.[2] Crucially, significantly fewer men with TV < 4 mL are able to develop sperm in the ejaculate compared to those with some spontaneous puberty (68% [CI: 58-77] vs 84% ([CI: 76-89], $P = 0.011$.[14] Furthermore, CHH men with smaller testes (<4 mL) are much more likely to have had cryptorchidism. These observations are in line with maldescended testes being a negative predictor of fertility. Thus, patients with a history of cryptorchidism typically require longer treatment to achieve spermatogenesis.[19,20] Moreover, while 75% (CI: 69-81) of men with CHH can develop sperm in the ejaculate on gonadotrophin therapy, sperm counts are lower compared to men with no prior spontaneous pubertal development (TV < 4 mL), ie, 3.37 (2.25-4.49) vs 12.94 (8.00-17.88) × 10^6/mL, $P < 0.0001$.[14.]

6.3 | Sequential gonadotrophin therapy: FSH pre-treatment followed by FSH + hCG

Summarising the data on hCG monotherapy and combined gonadotrophin therapy illustrates why TV is a key predictor of fertility outcome. Approximately 90% of testicular volume is determined by the seminiferous tubules. Thus, factors that promote seminiferous tubule development (ie, proliferation of Sertoli and germ cells), are critical for optimising spermatogenic capacity.[5] A plausible approach to improve fertility in men with CHH and severe GnRH deficiency is to replicate the gonadotrophin profile of early puberty (ie, increased FSH prior normal T concentrations). Administering unopposed FSH treatment prior to the addition of hCG, may provide maximal opportunity for proliferation of immature Sertoli and germ cells prior to maturation that follows hCG-induced T secretion.[5]

Follicle-stimulating hormone promotes Sertoli cell development yet has negligible effects on Leydig cell stimulation and T secretion. This holds true even when administering hMG—whose LH component is crucial to ovulation-induction in HH women, but non-significant in respect of testicular T secretion.[2] Several studies have demonstrated the beneficial effect of FSH pre-treatment on a variety of HH states including severe GnRH deficiency.[5,21-23] Subcutaneous injections of FSH (75-150 IU) daily or every other day effectively induces Sertoli and germ cell proliferation and testicular growth.[5] After 2-4 months of unopposed FSH, hCG-induced T production induces cell maturation and initiates the process of spermatogenesis. Men may choose to cryopreserve (bank) sperm for future ICSI—or intrauterine insemination (IUI) if sperm concentration is sufficient.

Given the rarity of CHH, recruiting adequate numbers of patient's is difficult, limiting statistical power. Therefore, it is challenging to definitively demonstrate whether the sequential approach is unequivocally superior to combined gonadotrophin therapy—even in respect of achieved sperm counts, let alone the key hard end-point of live birth rate (with-and without- need for ART). Nevertheless, for men with CHH and TV < 4 mL, there is clearly no role for an initial hCG monotherapy phase. Often, CHH patients and clinicians struggle anyway to achieve satisfactory serum T concentrations during hCG monotherapy. Further, such an approach may inadvertently result in premature maturation of a depleted pool of unproliferated Sertoli and germ cells. In clinical practice (as opposed to clinical trials), peak sperm concentration may not be attained as the female partner may become pregnant (either naturally or via ART).

6.4 | Previous testosterone treatment

A single retrospective study found prior testosterone treatment be an adverse prognostic marker for achieving spermatogenesis in HH,[24] but reassuringly this effect was not observed in a subsequent large meta-analysis.[14] The original observation likely arose from a confounding factor—that men with a more severe forms of HH (and therefore, a poorer prognosis for spermatogenesis-induction) may be more likely to have received testosterone prior to being offered spermatogenesis-induction therapy. While this question remains to be definitively addressed, a recent meta-analysis failed to demonstrate any effect of prior testosterone treatment on fertility outcomes [14.]

Drug licensing studies in the area of spermatogenesis-induction in HH have typically required men to have be off testosterone replacement for a sufficiently long period (ie, 6 formulation-dependent half-lives) to biochemically re-confirm diagnosis of HH prior to enrolment.[16,17] For men receiving long-acting formulations, such as testosterone undecanoate 1 g depot, such pre-trial requirements prevent these patients from participating.[25] However, in clinical contexts, men with HH typically develop unwanted symptoms during prolonged washout periods, and no data support an arbitrary period off testosterone prior to initiating gonadotropin therapy.

Nevertheless, persistence in the circulation of exogenously-derived testosterone will necessarily result in relative under-treatment with hCG (whose dose is primarily determined by titration to achieve normal range serum levels of Hb, T & E2). Under these circumstances, there is a theoretical risk of Sertoli cells not being exposed to the full paracrine T levels required for spermatogenesis. Therefore, when spermatogenesis-induction is first considered, it seems sensible to convert patients from long-acting depot to shorter-acting T preparations at least 6 months prior to the anticipated treatment start date.

6.5 | Monitoring

Careful clinical and biochemical monitoring by clinicians experienced in these specific fertility induction protocols is essential. Regular assessment of TV using a Prader orchidometer is important to evaluate testicular growth. It is worthwhile to note that clinical measurement tends to slightly overestimate TV—particularly at small volumes. Accordingly, calculated TV using sonography in 3 planes provides more sensitive, reliable and objective measures.[26]

Patients should be informed of potential adverse effects of fertility-inducing treatment. Gynaecomastia is seen in up to one-third of patients as a result of excess hCG-induced oestradiol-secretion.[2,10] Elevated haematocrit is also a common adverse effect of hCG and should be monitored closely during therapy. Such unwanted effects can be avoided or minimised by lowering the hCG dose. Titration can sometimes be challenging when striking a balance between reaching optimal serum T concentration and avoiding adverse effects. In some cases, it may be necessary to accept slightly sub-normal serum T concentration, along with lower patient-reported energy levels and/or libido, in order to avert gynaecomastia or erythrocytosis. The half-life of hCG is approximately, 36-hours so trough testosterone and oestradiol concentrations (obtained prior to the subsequent injection) are most informative for ensuring that target T concentration is being maintained.

Patients should be given clear, detailed instruction and be able to demonstrate aseptic self-injection technique. While most patients are highly motivated to closely follow fertility-inducing regimens, therapeutic adherence should be assessed at each and every visit. Notably, spermatogenesis can occur even in the setting of modest TV. Therefore, seminal fluid analysis should be performed once a TV of 5-8 mL is attained with repeat analysis every 2-3 months thereafter. There also needs to be a regular process of discussion with both the couple and the fertility specialist in respect of how long to proceed with attempted natural conception before moving on to ART. Those men with a history of bilateral cryptorchidism and TV < 4 mL are more likely to remain persistently azoospermic despite optimal therapy and consultation with a clinical expert in micro TESE may be warranted.

6.6 | Gonadotrophin dose titration

6.6.1 | hCG

A typical hCG starting dose is between 3000-5000 IU per week, divided into at least 2 injections to ensure relatively stable serum T concentration. Serum concentrations of T, Hb and E_2 should be measured every 4-6 weeks, with dose-adjustments made as needed until steady-state has been achieved. As the testes grow, it may be possible to slowly titrate-down the hCG dose while maintaining normal serum T concentration. Steady-state may sometimes be achieved with as little as 1000 IU per week. Failure to achieve normal serum T concentration may result from poor adherence,[27] or rarely, development of antibodies.[10] Currently, the greater expense and inherent wastage of the newer injection pen devices containing recombinant CG outweighs the convenience of being able to dial-up an exact dose.

6.6.2 | FSH

A starting dose of FSH is 75-150 IU every other day (or 3×/week) is used, with dose adjusted upwards if necessary to achieve serum FSH concentration in the physiologic range of 4-8 IU/L. Men with CHH have a limited Sertoli cell population and a low baseline I_B is expected. Monitoring serum I_B concentration can be informative for gauging response to FSH priming and may be considered as a proxy for the proliferation of immature Sertoli cells during FSH treatment.[2,5,10] Serum I_B levels typically plateau after 2 months of FSH treatment.[5] Sharing laboratory results and explaining biochemical changes with patients may help support adherence early in treatment when subtle changes in TV may not yet be clinically evident.

To date, no clear protocol has been established for men with a history of cryptorchidism. Some have posited that FSH pre-treatment could be prolonged until I_B concentration has plateaued, but extended FSH-only treatment results in patients being hypogonadal for a prolonged period. While not yet formally evaluated, exogenous testosterone (eg, transdermal gel) could potentially be used during FSH pre-treatment. This should not raise intra-testicular T concentration and, thus, Sertoli and germ cell proliferation could be supported whilst limiting hypogonadal symptoms (prior to adding hCG following FSH priming). However, such an approach should only be performed by clinicians with experience in fertility-inducing treatments for CHH.

6.7 | Continuation

Treatment is usually continued after conception, into the second trimester to sustain fertility in the event of miscarriage—which affects one-in-four pregnancies. If the couple desires to conceive again quickly, hCG alone can be continued to maintain spermatogenesis, though sperm count and TV tend to progressively diminish over time.[28] Prior gonadotrophin treatment results in a 2-3-fold shorter time to the appearance of first sperm on subsequent treatment cycles [29] yet the success of subsequent cycles cannot be guaranteed. A rational approach is to counsel patients on this and offer sperm cryopreservation (banking) prior to cessation of gonadotrophin therapy and transition to long term testosterone replacement.

7 | FUNCTIONAL HYPOGONADOTROPIC HYPOGONADISM

In some hypogonadal men, the hypothalamo-pituitary-testicular (HPT) axis is fundamentally intact, but there is a reversible environmental constraint on GnRH-mediated gonadotropin secretion. Salient examples of this include ongoing use of opiates,[30] ongoing or recent (within 1 year) use of androgens or anabolic steroids,[31] or a chronic bioenergetic deficit between energy intake and energy expenditure—[31] due to eating disorder, athletic endurance training or "food-faddism"—resulting in low fat mass and hypoleptinaemic HH, analogous to female hypothalamic amenorrhoea. In these cases, HH invariably resolves and spermatogenesis recovers upon removal or resolution of the constraint. Therefore, except when the female partner might be approaching the end of her reproductive lifespan,

HH management should focus on lifestyle-change rather than proceeding directly to gonadotropin treatment (hCG monotherapy).

The bulk of negative feedback exerted by testosterone on the HPT axis is mediated by aromatisation to oestradiol. Accordingly, men with functional HH may respond well to treatment with aromatase inhibitors (eg, anastrozole), or oestrogen antagonists—SERMs (eg, clomiphene), although evidence is limited with methodologically weak studies and use remains "off label" with no current product licenses.[32,33] Moreover, the effect on bone health with longer term treatment remains unanswered. Thus, caution is warranted when considering prescribing these agents to restore fertility in men with HH related to obesity, opioids or anabolic androgen abuse.

8 | TREATING COUPLES

Fertility (sperm) induction should be initiated and managed within the context of a multidisciplinary team including endocrinology, andrology and reproductive medicine specialists. Although our focus has necessarily been on technical aspects of spermatogenesis-induction in men with HH, we cannot over-emphasise the importance of evaluating the female partner at the outset. Confirming ovulation and tubal patency, providing pre-pregnancy counselling and optimising pre-existing medical conditions are all important aspects of comprehensive care. Moreover, a significantly higher "social" eligibility threshold currently applies to NHS funding of fertility treatments than for all other medical conditions, requiring both partners to have *indefinite* leave to stay in the UK. Andrological assessment is also vital to confirm the presence of the *vas deferens* before initiating treatment, as congenital absence of these structures can be associated with cystic fibrosis gene mutations, as well as giving rise to obstructive azoospermia.

While many HH men will develop sperm in the ejaculate, only half of sperm induction cycles result in natural pregnancy and approximately 10% of couples require ART,[24] typically involving controlled ovarian stimulation, oocyte retrieval and ICSI. Surgical sperm retrieval via microdissection and testicular sperm extraction (micro TESE) may be an option for men who remain azoospermic. Whilst it is important to give couples the opportunity for natural conception, combined gonadotrophin treatment cannot be an open-ended process, due to pragmatic issues of resource-utilisation, patient injection-fatigue and, potentially, the age of the female partner. If pregnancy has not occurred within a year of sperm first appearing in the ejaculate, then ART should probably be undertaken without too much delay. In that situation, sperm cryopreservation is indicated and consideration given to withdrawing gonadotrophin support thereafter.

Providing holistic care for the couple with the availability of counselling and psychological support is needed during treatment. Ongoing support and guidance are essential for couples who do not conceive after sperm induction. Additional counselling and decisional support are recommended to those couples opting for donor sperm, fostering or adoption as alternative methods of family formation.

9 | CONCLUSIONS

It is not uncommon for men with HH to be told at the time of diagnosis that they are irrevocably infertile. Thus, individuals may not present for fertility consultation as this is considered a "lost cause". In truth, HH is one of the few treatable forms of male infertility. For men with partial or full testicular development, hCG monotherapy initiated by clinicians knowledgeable in gonadotrophin therapy can be highly effective. Similarly, men with severe HH (TV < 4 mL) sequential treatment can offer possibilities for fertility. While men with HH may not reach quantitatively normal semen parameters by WHO criteria, this does not preclude natural fertility. Therefore, from at the outset of treatment it is imperative that a pragmatic approach to the duration of treatment is agreed considering the likelihood of normal spermatogenesis, the partner's fertility potential and the facility for sperm cryopreservation as well as the prospects for and availability of ART. Treatment must be within the context of an experienced multidisciplinary team to ensure appropriate investigation, counselling, gonadotrophin treatment and timely referral for assisted reproduction if necessary.

ORCID

Matthew Prior http://orcid.org/0000-0003-2129-1073
Jane Stewart http://orcid.org/0000-0003-4301-8481
Richard Quinton http://orcid.org/0000-0002-4842-8095

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How to cite this article: Prior M, Stewart J, McEleny K, Dwyer AA, Quinton R. Fertility induction in hypogonadotropic hypogonadal men. *Clin Endocrinol (Oxf)*. 2018;89:712–718. https://doi.org/10.1111/cen.13850