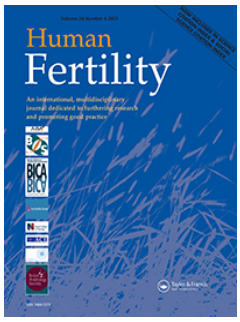

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REVIEW ARTICLE

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Management of congenital hypogonadotropic hypogonadism in females

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ABSTRACT

This review explores the challenges in the diagnosis of hypogonadotropic hypogonadism, the transition of care from paediatric to adult care and the considerable health implications of this condition. The role gynaecologists and general practitioners have in managing hormone replacement therapy and reproductive potential is also highlighted. The fertility treatment options, which include ovulation induction with gonadotrophins and in-vitro fertilisation, are discussed in detail along with highlighting the fact that anovulation and markers of low ovarian reserve prior to priming treatment may not be reflective of poor reproductive potential. The holistic management of women with hypogonadotropic hypogonadism is still not standardised and evidence for subfertility management is scarce. This review aims to highlight this concern and provide guidance by evaluating current evidence.

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Hypogonadotropic hypogonadism; puberty; HRT; fertility

Introduction

Hypogonadotropic hypogonadism (HH) can be categorised by its pathophysiology into congenital hypogonadotropic hypogonadism (CHH), combined pituitary hormone deficiency (CPHD), and functional hypogonadotropic hypogonadism (FHH). It is characterised by hypothalamic-pituitary failure. From a reproductive health perspective, HH is classified as WHO type I ovulatory disorder and accounts for 10% of women with ovulation disorders (Kelberman & Dattani, 2007; Muñoz & Argente, 2002; Seminara et al., 1998).

Many articles discuss the management of HH as a whole group but each category is unique and each requires different approaches. The principal target of treatment in CHH is supplying exogenous gonadotrophin or sex steroid hormones depending on the timing and aim of treatment whether it is pubertal induction, general health, or fertility. The management of women with CPHD is distinctive from CHH because, in addition to the above management, they require extensive multidisciplinary input with endocrinologists to address the cause and the different pituitary functions affected, which can include HH, adrenal insufficiency, and hypothyroidism. CPHD can be congenital or acquired (Kelberman & Dattani, 2007).

In contrast, FHH is an acquired condition of hypothalamic suppression and is usually reversible as these women have an intact hypothalamic-pituitary-gonadal (HPG) axis. Recent evidence with the advance of genetic testing has shown that there is a genetic predisposition to FHH with links to rare sequence variants found in CHH or Kallmann Syndrome (Delaney et al., 2021). This translates into variability in individual susceptibility to stressors. The aim of FHH treatment is the correction of the underlying cause, which has led to an energy deficit or significantly stressed state. The state of energy deficit or stress can be triggered by eating disorders, excessive exercise, physiological stress, chronic illness, and drugs (Chan & Mantzoros, 2005; Dandona & Dhindsa, 2011; Dhindsa et al., 2004; Muñoz & Argente, 2002). Common drugs that can cause FHH include opiates, exogenous sex steroids, or dopamine antagonists. The treatment of both CPHD and FHH has a good prognosis.

This review focuses on women with CHH which represents the smallest group in the WHO Type 1 ovulatory disorder category. The incidence of CHH in women is 1 in 10,000 to 1 in 50,000 (Boehm et al., 2015; Shaw et al., 2011). Treatment in these women tend to be a longer process than the other categories and the prognosis may not be as good. CHH is a rare condition caused either by the absence of GnRH secretion from the hypothalamus or impaired GnRH action in the pituitary. The classical presentation is absent or

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incomplete sexual maturation, primary amenorrhoea and infertility, low sex steroids, and low or normal gonadotrophin level. CHH has a male predominance with a male to female ratio of 3:1 and when associated with anosmia it is termed Kallmann syndrome (KS) (Boehm et al., 2015). CHH may be associated with other developmental anomalies, such as renal agenesis, eye movement disorders, hearing loss, cleft lip or palate, dental agenesis, skeletal defects, intellectual impairment, and cardiovascular defect (Boehm et al., 2015; Quinton et al., 2001).

There are several challenges in the management of CHH. Diagnosis of the condition can be problematic as it may be difficult to distinguish from constitutional delayed puberty (Boehm et al., 2015). The transition from paediatric to adult care may pose problems and there are difficulties in ensuring an appropriate long term, lifelong care (Figure 1). The role of general gynaecologists and general practitioners in this transition of care, including the management of hormone replacement therapy and reproductive potential is essential to optimise patient care. This concerted effort aims to ensure optimal reproductive potential, bone, cardiac and psychological well-being of affected women.

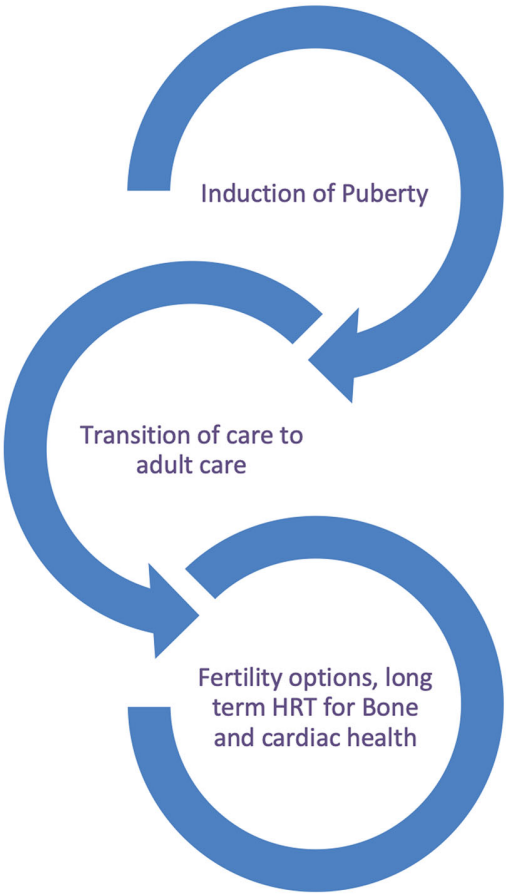

Figure 1. The transition of care from Paediatric to adult care is of paramount importance for effective long-term management and patient compliance.

The holistic management of women with CHH is not standardised and evidence for subfertility management is scarce. This review aims to highlight this concern and provide guidance by evaluating current evidence to assist these women to achieve their reproductive potential and maintaining good general health.

Diagnosis of CHH

It may be challenging to differentiate constitutional delay of growth and puberty (CDGP) from CHH. Currently, there are no testing criteria that achieve good discrimination and there may be significant overlap between patients with constitutional delay and those with hypogonadism. Approximately 35% of cases of delayed puberty in girls are attributed to CDGP. Both conditions present with absent or incomplete puberty, but CDGP is due to transient GnRH deficiency, which eventually reverses. In boys, inhibin B levels may differentiate these two clinical conditions, with the level of inhibin B reflecting the severity of FSH deficiency. However, further studies are required to ascertain the accuracy of inhibin B testing in girls. Currently, there is no diagnostic test with good specificity and sensitivity for girls (Boehm et al., 2015).

The diagnosis of CHH in most cases is made during late adolescence or early adulthood (Dwyer et al., 2016). However, this should not be accepted as normal and reflects a low index of suspicion by clinicians leading to delay in diagnosis. Efforts must be made to increase diagnostic accuracy as delay in management leads to significant psychological morbidity and long-term sequelae. 'Red flag' markers for congenital GnRH deficiency include strongly associated non-reproductive phenotypes: cleft palate/lip, syndactyly, hearing impairment, and anosmia; or a family history of CHH including the need for ovulation or spermatogenesis induction (Quinton et al., 2017). The presence of these features would increase the index of suspicion and earlier initiation of therapy.

The diagnosis encompasses clinical and biochemical pictures with absent or incomplete pubertal development along with low sex steroids (plasma oestradiol $<$20 pg/ml in females; equivalent to 74.38 pmol/L) and low or inappropriately normal gonadotrophin levels. The secretion of LH is found to be more significantly affected than FSH with otherwise normal pituitary function and a normal appearance of the pituitary and

hypothalamic region on magnetic resonance imaging (MRI). Exclusion of functional GnRH deficiency related to the nutritional deficit, excessive exercise, or stress is imperative (Boehm et al., 2015).

Traditionally, CHH has been considered a life-long condition. The spontaneous reversal has been documented in up to 10–20% of CHH patients (Dwyer et al., 2016; Raivio et al., 2007). However, the evidence for this is only convincing in men and this recovery may not be permanent (Sidhoum et al., 2014).

Genetics of CHH

CHH is genetically a heterogeneous disorder with identified X- linked, autosomal dominant, and autosomal recessive patterns of inheritance. More than 30 loci have been implicated in hypogonadotrophic hypogonadism. A comprehensive review has evaluated and listed the associated genes (Cangiano et al., 2021).

Recent developments have discovered oligogenicity in the inheritance of CHH genes. In oligogenic inheritance, two or more CHH gene mutations are found in one patient. Advances in the molecular basis of CHH have enabled the identification of genetic basis in 50% of cases (Cangiano et al., 2021). Genetic counselling should be considered in cases with a positive family history but is difficult in oligogenic inheritance due to variability in gene expression and penetrance.

Induction of puberty

Puberty is influenced by genetic and environmental factors and represents a dynamic phase of transition into adulthood to achieve maturity and reproductive potential. Puberty results from the reawakening of the HPG axis through the generation of GnRH pulses. Delayed puberty in girls is defined as the absence of pubertal onset by 13 years of age or absent menarche by age 15 in adolescent girls (Palmert & Dunkel, 2012).

The HPG axis is active in utero and shortly after birth (Brennan, 2013; Mogri et al., 2013). This phenomenon is referred to as mini-puberty and then becomes dormant for years (Morrison et al., 1994). At the onset of puberty, GnRH-induced pulses of LH are initially nocturnal and gradually extend to daytime as puberty progresses (Boyar et al., 1974; Dunkel et al., 1992; Wu et al., 1990). LH stimulates theca cells to produce androgens, which are aromatised into oestradiol from granulosa cells following FSH stimulation, along with the recruitment of secondary ovarian follicles. Inhibin B and AMH are produced by granulosa cells (Valeri et al., 2013). Circulating levels of inhibin B increase during puberty in girls whilst AMH concentrations show only minor fluctuations during female puberty (Hagen et al., 2010).

The aims of pubertal induction in CHH, are to achieve timely secondary sex characteristics which include breast and uterine development, to attain projected final height, acquire peak bone mass, optimise reproductive potential and maintain psychological well-being. It is important to recognise that randomised controlled trials on hormonal treatment in CHH are scarce, and data on clinical observational studies are also limited. Primary variables to determine the dose of hormone replacement therapy are age, patient satisfaction and clinical response.

The transition from childhood into adulthood is a dynamic process involving various complex hormonal, behavioural, physical, and cognitive changes. There is a dearth of evidence regarding optimal age for initiation of oestrogen replacement. Decisions should be made according to the natural age of onset of puberty and risks associated with delayed initiation of hormone replacement in relation to uterine, cardiac, and bone health. Low dose oral or transdermal oestradiol is recommended to mirror the normal stages of pubertal development. These doses are gradually increased to mimic normal puberty and prevent premature epiphyseal closure (Rosenfield et al., 2005).

The Royal College of Obstetricians and Gynaecologists advises starting exogenous oestrogen regimens at age 12 due to the risk of premature epiphyseal closure ('Sex Steroid Treatment for Pubertal Induction and Replacement in the Adolescent Girl-Scientific Impact Paper No. 40,' Royal College of Obstetricians and Gynaecologists, 2013). However, more recent evidence in other congenital hypogonadal conditions such as Turner's syndrome shows that low dose oestrogen started earlier at age 11 is used to achieve optimal uterine development (Klein et al., 2018). Therefore, treatment can be started earlier to optimise effects when undertaken with appropriate supervision to avoid the risk of premature epiphyseal fusion. The limiting step to this is the high proportion of girls with delayed diagnosis of CHH.

17B-oestradiol is the choice of oestrogen replacement compared to ethinyloestradiol (EE) and conjugated equine oestrogen (CEE) because it is a bioidentical hormone, causes smaller impairment of GH-mediated insulin-like growth factor 1 synthesis, and carries a lower risk of venous or arterial thrombosis (Dunkel & Quinton, 2014). 17B-oestradiol also allows monitoring of serum oestradiol levels.

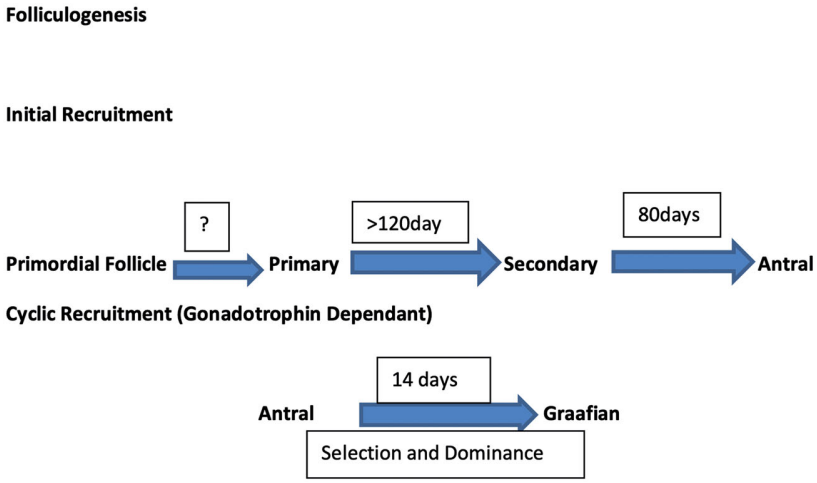

Figure 2. Folliculogenesis involves initial recruitment and cyclical recruitment phases. The antral stages of follicular development provide a target for exogenous or endogenous FSH to stimulate all or part of the present follicles into dominant follicle growth.

The transdermal route is preferred as it enables smaller dosage use, by dividing a patch into quarters compared to splitting tablets (Santen et al., 2010). Paediatric oral doses are not available in the UK. The dose generally starts at 6.25 mcg or 12.5 mcg in older girls (Dunkel & Quinton, 2014). The timing of dose escalation is dependent on the growth potential and is individualised.

Most breast development occurs in the two years of unopposed oestrogen prior to menarche. It has been stated that progesterone should be deferred until after adequate development of breast and uterus are achieved or with first breakthrough bleeding (Shifren, Gass, & NAMS Recommendations for Clinical Care of Midlife Women Working Group, 2014). However, if at first breakthrough bleed, B4 breast development or mature sonographic uterine dimensions have not been achieved, a rational approach is to slightly reduce oestradiol dose whilst continuing to defer progesterone treatment. Cyclical progestogens found in pre-packed preparations for post-menopausal women can be used or prescribed separately for 12 to 14 days in each cycle.

The combined oral contraceptive pill's (COCP) relatively higher dose of oestrogen and progestogen in early puberty would disrupt breast development causing breast hypoplasia, leading to early epiphyseal closure and reduced bone mass (Matthews et al., 2017). Although COCP is commonly used as HRT after puberty, its use is not endorsed by the European Consensus Guidelines for CHH, which instead recommends oestradiol-based HRT (Boehm et al., 2015). Evidence suggests that COCP does not provide optimal oestrogen replacement in young women post-puberty and the use of COCP represents inadequate treatment in these women (O'Donnell et al., 2012; Swee et al., 2019).

Absorption of both transdermal and oral oestradiol is significantly variable between each woman. Therefore, these women need personalised treatment with dose adjustments according to serum oestradiol measurements. The use of 17B-oestradiol allows monitoring of serum oestradiol levels. This enables dose adjustment to maximise effects on bone densitometry, cardiovascular health, and fertility. The required dose is higher than what is found in standard menopausal HRT (Swee et al., 2019).

Bone health

Maintenance of bone health is crucial for women with HH. Oestrogen plays an important role in bone remodelling, not only by its effect on osteoblasts and osteoclasts but also via autonomic pathways involving beta2 adrenergic receptors. Delaying oestrogen replacement is deleterious to bone health as this leads to osteopenia and osteoporosis (Benetti-Pinto et al., 2002; Cartwright et al., 2016; Gussinyé et al., 2000). Transdermal oestrogen use in women with premature ovarian insufficiency is found to have a better effect on bone mineral density than the use of the oral contraceptive pill (Herrmann & Seibel, 2010; Lopez et al., 2014; The European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI et al., 2016). Moreover, oral oestrogen was not reported to be effective in increasing bone mineral density (BMD), which may be explained by its effect on decreasing insulin-like growth factor 1 (IGF1) production by the liver (Weissberger et al., 1991). Transdermal oestrogen replacement has been found

to increase spine and hip BMD and prevent the decline in BMD Z Score in patients with anorexia nervosa (Misra et al., 2011). The fixed-dose HRT regimens used in published studies pose a key limitation. HRT regimens that are monitored to target physiological oestradiol levels in individual subjects would provide better optimisation of bone density outcomes. Baseline BMD assessment should be carried out at attainment of final height.

Cardiovascular health

Oestrogen has a cardio-protective effect on the myocardium and blood vessels, reducing the risk of ischaemic heart disease. Ahmed et al. (2008) reported that low oestradiol level <50pg/ml (the equivalent of 184 pmol/L) along with low FSH and LH (<10IU/L) was found in women with angiographic evidence of coronary disease in comparison to premenopausal women with normal angiography (Ahmed et al., 2008). Early hormone replacement can prevent morbidity and mortality associated with ischaemic heart disease in patients with CHH.

Fertility treatment

In CHH patients, lack of gonadotrophins leads to failure of follicular maturation and thus, anovulation (Figure 2). Furthermore, in women with CHH, the ovarian volume, antral follicle count, and AMH levels do not predict treatment response (Bry-Gauillard et al., 2017; Chan & Liu, 2014). AMH levels are lower in these women than in normal patients and represent the prolonged duration of FSH deficiency. However, it is important to stress that the lack of ovulation or a low AMH level does not reflect poor ovarian reserve and in most cases, replacement therapy leads to successful fertility treatment (Deubzer et al., 2014).

It has been shown that a low AMH level in CHH women is reversible with the use of gonadotrophin administration (Chan & Liu, 2014). AMH production is dependent on FSH. Throughout folliculogenesis, AMH is produced by follicle granulosa cells in primary, secondary, pre-antral, and early antral follicles which are being recruited. Therefore, the administration of FSH in CHH women may increase AMH levels by promoting folliculogenesis. AMH production is absent in primordial follicles and declines in the dominant follicle phase (Dewailly & Laven 2019).

Initial fertility work-up for these women should include assessment of tubal patency, uterine integrity, and male factor evaluation. Fertility in this group of women is dependent on establishing the non-functioning HPO-axis caused by a deficiency in gonadotrophins. Therefore, there is no role for simple agents such as clomiphene citrate. The first-line treatment is ovulation induction using pulsatile GnRH or gonadotrophins (Silveira & Latronico, 2013).

GnRH treatment for fertility

Pulsatile gonadotropin-releasing hormone (GnRH) treatment is a logical and effective means to establish normal ovarian function. It has the advantage of mono-follicular development and normal luteal phase function, but some do not consider it a patient-friendly option because of the need to carry a pump continuously (Kaufmann et al., 2007; Yasmin et al., 2013). Pulsatile GnRH is also not available in all countries. Patients generally prefer daily gonadotropins injections although this option carries an increased risk of multiple follicular growths and ovarian hyperstimulation due to supraphysiological stimulation of follicular growth (Balen et al., 1994; Krause et al., 2009).

Gonadotrophin ovulation induction

As depicted in the two cells and 2-gonadotrophin theory (Short, 1962) both FSH and LH are required for folliculogenesis. LH stimulates theca cells to produce androgens from cholesterol and FSH facilitates the conversion of these androgen precursors into oestrogen by aromatisation (Short, 1962). CHH women do not have endogenous LH, therefore a gonadotrophin with an LH component is required. The choice of gonadotrophin to be used in these women is Human menopausal gonadotrophin (hMG) that contains FSH and LH in a ratio of 1:1 or recombinant FSH and LH (Couzinet et al., 1988; Schoot et al., 1994).

Women with CHH require priming due to the prolonged deficiency in gonadotrophins. At the initiation of treatment, is it very common to have low AFC and AMH levels due to the long-term absence of FSH follicular stimulation. A prolonged, low oestrogenic state will also affect fertility, as it is associated with an underdeveloped uterus. Therefore, these women may require simultaneous ovarian priming for follicular development and uterine priming. Highly purified hMG or recombinant FSH and LH are used for ovarian priming and oestrogen for uterine priming. However, the evidence for oestrogen use in uterine priming is not strong.

Women with absolute GnRH deficiency generally take longer to respond as the pituitary needs to be

primed for several days or weeks before active secretion of oestradiol (Yasmin et al., 2013). It is not uncommon for the priming of the ovaries and uterus to need treatment for 12 weeks prior to ovulation induction. Priming is initiated by low dose gonadotrophin, followed by weekly scans for uterine, ovarian, and endometrial assessment. Biochemical markers, which include oestradiol and AMH, provide information about the effectiveness of priming. The dose can be increased or decreased according to the response. However, it is prudent to resist the temptation to increase doses too early and look for a rise in AMH as the first sign of follicular activity. The following diagrams illustrate the development of ovarian follicles and the targeted period of gonadotrophin dependent follicular growth in the last three months.

Patients must be informed of the duration of treatment to increase compliance and reduce feelings of disappointment. It can be emotionally difficult for patients as scan findings and biochemical markers do not show significant change initiatives.

Dubourdieu et al. (2013) suggested the ovarian response rate to GnRH pulsatile treatment was 73% and to gonadotrophin treatment was 60%; while clinical pregnancy rate was 45% and 15% respectively. However, various studies have reported a 74–87% follicular growth rate and 22% pregnancy rate with the use of gonadotrophins.

In a recombinant LH study of patients with HH, the recommended optimal LH dose was 75 IU. When the LH dose was 75 IU, there was 88% follicular growth, which increased to 100% at 225 IU; but the fertilisation rate decreased when 225 IU LH was used (LH ceiling theory) (The European Recombinant Human LH Study Group, 1998). A small study based on 35 women with HH by Carone et al. (2012) reported that ovulation induction was similar in highly purified hMG and a recombinant FSH and recombinant LH regime. However, this small study found the recombinant regime to have significantly improved pregnancy rate to highly purified hMG.

The cumulative pregnancy rate over six cycles of ovulation induction is about 60–70% (Jindal & Jindal, 2015). Historic evidence has shown with the introduction of gonadotrophic ovulation induction regimes, women with CHH can expect near normal fecundity (Overton et al., 2002). Following ovulation, these patients require luteal support in the form of oestradiol and progesterone until 12 weeks gestation; or in the case of repeated hCG for luteal support until a pregnancy test is positive to support the corpus luteum.

If women wish to breastfeed, they can be advised to restart low dose oestradiol after delivery at an oral dose of 0.5 mg or 25 mcg patch. After breastfeeding, patients can return to their original oestrogen and progesterone hormone replacement regimen.

In vitro fertilisation (IVF)

In CHH patients who do not respond to gonadotrophin ovulation induction or patients with a tubal factor or significant male factor, IVF is the best option. A systematic review and meta-analysis of retrospective trials to determine the effect of IVF on the fertility of CHH patients were performed by Gao et al. (2018). They concluded that IVF is a viable treatment option after long-term gonadotrophic treatment for ovulation induction in CHH women. A total of 11 trials were included with a total of 475 women. Nine of these trials contained control groups which comprised 659 cases. The control groups consisted of couples with tubal factors, male factors, or unexplained infertility. A combination of hCG with hMG was used in five trials and the average duration of stimulation across all the trials was two weeks. The pregnancy rate for CHH women was reported at 48%. They showed no difference from other cohorts in terms of fertilisation rate, implantation rate, live birth rate or adverse events. The limitations of this systematic review were the small sample size, availability of only retrospective studies, and poor description of baseline characteristics or prior gonadotrophin priming for ovulation induction in CHH women.

Yilmaz et al. (2015) compared IVF in HH and patients with mild male factors in a retrospective study of 80 patients. In the study, the diagnostic criteria for HH included serum levels of FSH <2.5 IU/L, and primary or secondary amenorrhoea with the absence of withdrawal bleeding following progesterone challenge. They found no difference in total oocyte number collected or pregnancy rate. However, this study reported the duration of stimulation was slightly longer in HH patients at 12.5 ± 2.06 days compared to 10.08 ± 1.62 days in the MF infertility patients ($p = 0.001$). They concluded that the response to controlled ovarian hyperstimulation treatment is similar in both groups (Yilmaz et al., 2015). Similarly, Ulug et al. (2005) and Yildirim et al. (2010) suggested that the results of ART in CHH patients treated with HMG were comparable to those in women with tubal factor infertility and unexplained infertility.

Jiang and Kuang (2018) presented a retrospective cohort study suggesting low-dose hCG combined with

hMG for HH women undergoing ovarian stimulation in IVF provides favourable pregnancy rates. Low dose hCG appeared to reduce HMG duration. However, further studies are required to confirm refuting the routine use of low dose hCG.

Due to the lack of gonadotrophins in CHH women, only hMG or recombinant FSH and LH should be used and there is no requirement for GnRH analogues or antagonist to prevent premature ovulation in their IVF cycles. These women will also need extended luteal support in the form of oestrogen and progesterone from egg collection to 12 weeks in ongoing pregnancies as described previously in gonadotrophic ovulation induction.

Psychological support

CHH patients can have low self-esteem, distorted body image, impaired psychosexual development and, in some cases, problems with sexual identity (Dwyer et al., 2016). In such cases psychological and peer support should be strongly considered.

Future considerations

Identifying biomarkers to facilitate early diagnosis can significantly improve care by initiating early treatment. Genetic testing can be informative in cases with positive family history. The optimal route, dosage, and regimens for pubertal induction need further study and standardisation with reference to pubertal development, uterine growth, bone health, and psychosocial measures. The transition of care between paediatric and adult is important for the continuation of treatment. General practitioners and gynaecologists play a role in recognising and supporting this transition. Effective patient communication, therapeutic education, and shared decision-making are key elements for ensuring compliance.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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