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The use of hormone stimulation in male infertility

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Abstract

Infertility affects 15% of couples worldwide and in approximately 50% of cases the cause is secondary to an abnormality of the sperm. However, treatment options for male infertility are limited and empirical use of hormone stimulation has been utilised. We review the contemporary data regarding the application of hormone stimulation to treat male infertility. There is strong evidence supporting the use of hormone stimulation in hypogonadotropic hypogonadism but there is inadequate evidence for all other indications.

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Keywords

Hormone Stimulation Therapy, Male Infertility, Azoospermia, Hypogonadotropic Hypogonadism, Hypergonadotropic Hypogonadism, Eugonadism, Gonadotropin Releasing Hormone, Gonadotropins, Selective Oestrogen Receptor Modulators, Aromatase Inhibitors, Dopamine Agonists.

Introduction

Infertility is the inability of a couple to achieve spontaneous clinical pregnancy despite one year of regular, unprotected, sexual intercourse [1]. Infertility affects 15% of couples worldwide [2,3]. Of these cases, 20–50% are secondary to a male factor [4]. Male factor infertility is defined as the abnormality of semen analysis according to the World Health Organisation guidelines for semen parameters (Table 1) [1,5]. The aetiology of male factor infertility can be categorised by the anatomical level of the abnormality (Figure 1) [6]. Up to 40% of cases are idiopathic [6].

Male infertility is on the rise and there is data showing a deterioration of sperm quality from 1982 to 2022 [7–10] Male infertility has become the leading cause for vitro fertilisation (IVF) in the UK [11]. It is unclear why male infertility is increasing but rising levels of obesity and endocrine disruptors have been implicated [12–14]. Male infertility has also been associated with poorer general [15] and psychological health and holds a societal stigma associated with domestic violence [16].

Treatment options for male infertility are limited to assisted reproductive technologies (ARTs), namely in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). Both ICSI and IVF success rates in male infertility are similar and align with the global average of 35% [17–19]. Moreover, each cycle of ART has been estimated to cost on average £3348 [20]. Healthcare resource management in the UK has resulted in restrictions on eligibility and funding for ART cycles [21,22].

The most severe manifestation of male infertility is azoospermia, the absence of sperm in the ejaculate. Azoospermia has been estimated to affect 1% of men, and 10–20% of males presenting to infertility clinics [23]. Azoospermia is classified as obstructive (OA) if there is a blockage to the conduit of the sperm or non-obstructive (NOA) when the is an impairment of

Table 1

A table showing the World Health Organisation (WHO) semen parameter reference values previously used in the diagnosis of male infertility [5].

Semen Parameter	Reference Value (95% CI)
Semen Volume: ml	1.5 (1.4–1.7)
Sperm Concentration: 10^6/ml	15 (12–16)
Total Sperm Number: 10^6/ejaculate	39 (33–46)
Morphology: % normal forms	4 (3.0–4.0)
Progressive Motility: %	32 (31–34)
Total Motility: %	40 (38–42)
Vitality: % live	58 (55–53)

Table 2

A table displaying all the studies investigating the efficacy of hormone stimulation therapy in patients with hypergonadotropic hypogonadism and Eugonadism.

Study (Year)	Study design	Population	Intervention Regime	Hormone changes	Rates of Sperm returning to the ejaculate/Surgical Sperm Retrieval (NOA Patients only)	Pregnancy Live birth rates	Adverse Events
Hypergonadotropic Hypogonadism							
Shiraishi et al. (2012) [251]	Case control	cHH NOA (n = 48) Intervention (n = 28) Control (n = 20)	5000 IU hCG 3 times a week for 4–5 months (n = 13) ***or*** 5000 IU hCG 3 times a week for 5 months ***and*** 150 IU FSH 3 times a week for 2 months (n = 15) Control group: no treatment	hCG only cohort: - Increased tT from baseline (*p<0.01*) - Decreased LH from baseline (*p<0.05*) - FSH unchanged hCG and FSH cohort: - Increased tT from baseline (*p<0.0001*) - Decreased LH and FSH from baseline (both *p<0.0001*)	SSR via mTESE: Intervention group: 6/28 (21.4%) Control group: 0/20 (0%) (*p<0.05*) Increased SSR associated with hypospermatogenesis (*p<0.05*)	NR	Acne: 3/28 (10.7%) Gynecomastia 2/28 (7.1%)
Shiraishi et al. (2016) [253]	Case series	cHH NOA (n = 21)	5000 IU hCG 3 times a week for 4 months ***and*** 150 IU FSH 3 times a week for 3 months Total duration: 4 months	Increased tT and E2 from baseline (both *p<0.01*) Decreased FSH and LH from baseline (both *p<0.01*)	SSR via mTESE: 2/21 (9.5%) Increased SSR associated with hypospermatogenesis and late maturation arrest (*p<0.01*)	PR: 1/21 (4.8%) LBR: 1/21 (4.8%)	Acne: 3/21 (14.3%)
Hu et al. (2018) [252]	Case control	cHH NOA (n = 35) Intervention (n = 25) Control (n = 10)	3.6 mg Goserelin once every 4 weeks for 6 months ***and*** 2000 IU hCG once a week for 5 months ***and*** 150 IU hMG twice a week for 4 months Control group: no treatment	Intervention group: Increased tT from baseline (*p<0.05*) Decreased FSH and LH from baseline (both *p<0.001*)	Rate of sperm in the ejaculate: Intervention group: 1/25 (4%) Control group: 0/10 (0%) - Mean sperm conc: 1.42×10^6/ml - Mean total sperm count: 3.98×10^6 SSR via mTESE: Intervention group: 1/25 (4%) Control group: 0/25 (0%)	NR	Symptoms of androgen deprivation (e.g erectile dysfunction) on Goserelin: 10/25 (40%) - resolved with hCG Did not tolerate treatment: 10/25 (40%)

Pavlovich et al. (2001) [255]	Case series	HH NOA (n = 43) ***and*** Oligospermia (n = 20)	Testolactone 50 mg twice daily for mean duration 5 months If oestradiol still high after 1 month, then Testolactone 100 mg twice daily Mean treatment duration: 5 months	Increased mean tT (*p<0.01*) and T:E (*p<0.01*) from baseline Decreased mean E2 (*p<0.01*) from baseline	Rate of sperm in the ejaculate: 0/12 (0%)	NR	Asymptomatic deranged LFTs 8/43 (18.6%) - resolved on cessation of therapy
Saylam et al. (2011) [256]	Case series	HH NOA (n = 17) ***and*** Oligospermia (n = 10) (all T:E < 10)	Letrozole 2.5 mg once daily for ≥6 months Mean treatment duration: 6.59 ± 0.88 months	Increased tT and T:E from baseline (*p=0.001*) Decreased E2 from baseline (*p=0.001*) LH and FSH no change	Rate of sperm in the ejaculate: 4/17 (23.5%)	NR	Mild headaches: 2/27 (7.4%)
Cavallini et al. (2013) [257]	RCT	HH NOA (n = 11) ***and*** Cryptospermia (n = 35) Intervention (n = 22) *HH NOA (n=6)* *Cryptospermia (n=16)* Control (n = 24) *HH NOA (n=5)* *Cryptospermia (n=19)*	Letrozole 2.5 mg once daily for 6 months Control group: placebo	Intervention group: Increased tT, FSH, and LH at 3 and 6 months (all *p<0.01*) Control group: no change	Rate of sperm in the ejaculate: Intervention group: 6/6 (100%) Control group: 0/5 (0%)	PR: 0/46 (0%)	Loss of libido, loss of hair, + cutaneous rash: 4/22 (18.2%) - dropped out of study
Shoshany et al. (2017) [258]	Case series	HH NOA (n = 28) ***and*** Men with normal and abnormal semen parameters (n = 58)	Anastrozole 1 mg once daily for 4 months	Increased LH, FSH, tT, and T:E at 3 weeks (all *p<.0001*) Decreased E2 at 3 weeks (*p<.0001*)	Rate of sperm in the ejaculate: 0/28 SSR via mTESE (n = 11) 8/11 (72.7%) 17/28 did not undergo surgery	NR	Joint pain, lower limb swelling, low libido, ocular pruritus/pain, depression, mastalgia, + dry mouth: 8/86 (9.3%) - treatment stopped in affected patients
Reifsnyder et al. (2012) [260]	Case control	HH NOA (n = 348) Intervention (n = 307) Control (n = 41)	Regimes unspecified Anastrozole (n = 180) Anastrozole + hCG (n = 29) CC (n = 66) Testolactone (n = 14) Testolactone + hCG (n = 12) hCG (n = 9) Other combinations/unknown (n = 38) Minimum treatment duration: 2–3months Control group: mTESE only	Decreased post-treatment FSH in intervention group compared to control (*p=0.02*)	SSR via mTESE Intervention group: 157/307 (51.1%) Control group: 25/41 (61.0%) (*p=0.31*) No association between SSR and response to therapy in intervention group (resultant tT > 250 ng/dl) (*p=0.97*)	No significant difference in, PR and LBR	NR

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Table 2. (*continued*)

Study (Year)	Study design	Population	Intervention Regime	Hormone changes	Rates of Sperm returning to the ejaculate/Surgical Sperm Retrieval (NOA Patients only)	Pregnancy Live birth rates	Adverse Events
Majzoub et al. (2016) [259]	Case Control	HH NOA (n = 20) Intervention (n = 16) *- Group A1 (n=10)* *- Group A2 (n=6)* Control (n = 4)	Intervention group: - Group A1: Anastrozole 1 mg once daily, 6 months - Group A2: CC 25 mg once daily and hCG 5000 IU once weekly (no treatment duration specified) Control group: no treatment	Statistically significant increase in Testosterone in intervention group compared to controls (*p=0.01*), but no difference in FSH and LH.	SSR via mTESE Intervention group: 6/16 (37.5%) Control group: 0/4 (0%)	PR: 3/16 (18.8%) LBR: 3/16 (18.8%)	NR
Amer et al. (2020) [261]	Case control	HH NOA (n = 40) Intervention (n = 20) Control (n = 20)	250 mg testosterone enanthate once a week for 1 month Then 5000 IU hCG once a week, 150 IU puFSH three times a week, and 250 mg testosterone enanthate once a week for 3 months	No statistically significant difference in baseline FSH between the two groups ($p = 0.946$)	SSR via mTESE: Intervention group: 2/20 (10%) Control group: 0/20 (0%) (*p=0.072*)	NR	NR
Sujenthiran et al. (2019) [262]	Case series	HH NOA (n = 23) Intervention (n = 15) Control (n = 8)	Intervention group: CC or hCG and FSH. Control group: no treatment	NR	SSR via mTESE: Intervention group: 6/15 (40%) Control group: 1/8 (13%)	Intervention group: PR: 4/15 (26.7%) LBR: 3/15 (20%)	NR
Peng et al. (2022) [250]	Case control	HH NOA (n = 569) Intervention (N = 395) Control (n = 174)	2000IU hCG IM every 2 days for first month After one month if FSH >11.1 u/L then hCG continued. If FSH 0.7–11.1 u/L then alternating 150IU puFSH and hCG every 2 days	NR	Rate of sperm in ejaculate: Intervention group: 27/395 (6.8%) Control group: 0/174 (0%) SSR via mTESE: Intervention group: 115/368 (31.2%) Control group: 34/174 (19.5%) (*p=0.006*)	PR Intervention group: 62/124 (50%) Control group: 19/35 (54.3%) LBR: Intervention group: 54/107 (50.5%) Control group: 14/31 (45.2%)	NR

Kohn and Herati (2021) [263]	Case series	HH NOA (n = 22) No prior treatment (n = 9) Previously treated (n = 13)	Testosterone enanthate once a week and 500IU hCG three times a week Then increased to 3000IU hCG 3 times a week 6 weeks before microTESE	NR	SSR via mTESE: No prior treatment: 7/9 (78%) Previously treated: 7/13 (54%) Not statistically significant (*p=0.38*)	NR	NR
Alrabeeah et al. (2021) [254]	Case control	HH NOA (n = 122) Intervention (n = 37) Control (n = 85)	CC 50 mg daily for 3–6 months prior to mTESE	FSH and LH higher in unsuccessful mTESE (n = 68) than successful mTESE (n = 54) cohort ($p < 0.05$). No difference in T levels (p = 0.793). No differences in FSH, LH, T between intervention vs control (p > 0.05)	SSR via mTESE: Intervention: 15/37 (40.5%) Control: 39/85 (45.9%) (*p=0.695*)	NR	NR
Eugonadism							
Aydos et al. (2003) [268]	Case control	NG NOA (n = 174) Intervention (n = 63) Control (n = 45)	Intervention: 75 IU FSH 3 times a week for 3 months Control group: no treatment	FSH Increase in intervention group vs controls (*p<0.001*)	SSR via cTESE: Intervention group: 40/63 (63.5%) Control group: 15/45 (33.3%) No significant difference. Increased SSR was associated with cohorts with focal spermatogenesis and hypospermatogenesis (*P<0.05*)	NR	No adverse effects observed
Selman et al. (2005) [269]	Case series	NG NOA (n = 49)	75 IU rFSH alternate days for 2 months 150 IU rFSH alternate days for 4 months From 4th month, hCG 2000 IU twice weekly for 2 months	NR	Rate of sperm in the ejaculate: 0/49 (0%) SSR via cTESE: 11/49 (22.4%)	PR: 3/49 (6.1%) LBR: 3/49 (6.1%)	NR
Efesoy et al. (2009) [270]	Cohort	NG NOA (n = 11)	100–150 IU FSH 2–3 times a week Mean treatment duration (7.45 ± 4.5 months)	Increase in FSH (*p=0.004*).	Rate of sperm in the ejaculate: 2/11 (18.1%) SSR via mTESE: 2/11 (18.1%)	NR	No adverse events observed

(*continued on next page*)

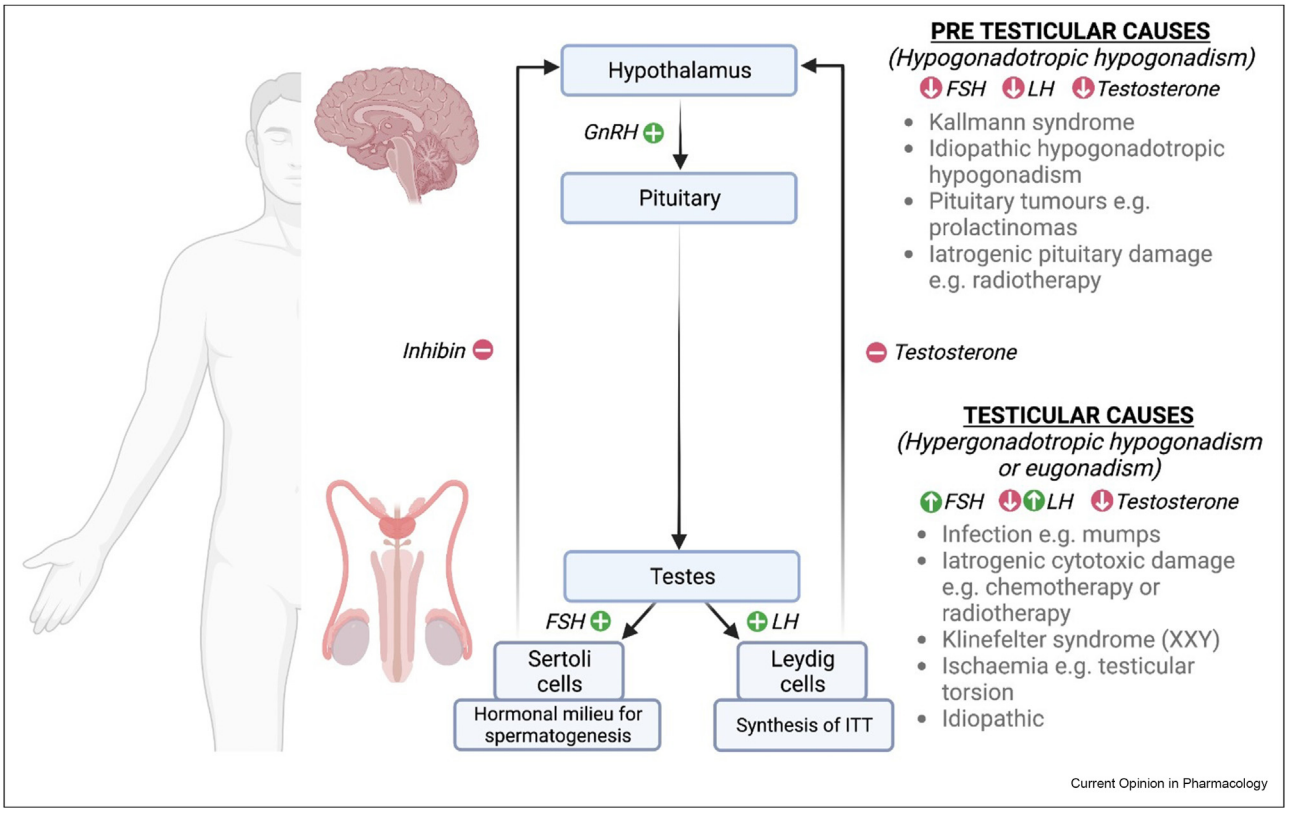
Table 2. (*continued*)

Study (Year)	Study design	Population	Intervention Regime	Hormone changes	Rates of Sperm returning to the ejaculate/Surgical Sperm Retrieval (NOA Patients only)	Pregnancy Live birth rates	Adverse Events
Gul et al. (2016) [271]	Case control	NG NOA (n = 83) Intervention (n = 34) Control (n = 49)	hCG 2500 IU twice a week for 10–14 weeks Control group: no treatment	NR	SSR via cTESE and mTESE: Intervention group: 17/34 (50%) Control group: 28/49 (57.1%) (*p=0.338*)	No significant difference in FR, PR and LBR	No adverse events observed
Cocci et al. (2018) [272]	Case Control	NG NOA (n = 50) Intervention (n = 25) Control (n = 25)	150 IU FSH, S.C. 3 times a week for 3 months. Control group (retrospective cohort): no treatment	NR	Rate of sperm in the ejaculate: Intervention group: 5/25 (20%) Control group: 0/25 (0%) (*p<0.05*) SSR via cTESE: Intervention group: 6/25 (24%) Control group: 2/25 (8%) (*p<0.05*)	Increased FR and PR in treated group vs controls (P < 0.05)	NR
Cavallini et al. (2011) [274]	Case series	NG NOA (N = 4)	Letrozole 2.5 mg, orally, once daily for 6 months	Increases in tT, FSH and, LH (*p<0.05 for all*). Oestrogen decreased (*p<0.01*)	Rate of sperm in the ejaculate: 4/4 (100%)	NR	Loss of libido, Cutaneous rash, and anxiety
Hussein et al. (2012) [273]	Case control	NGH NOA (n = 612) Intervention groups: (n = 496) *#1 (n=372)* *#2 (n=62)* *#3 (n=46)* *#4 (n=16)* Control (n = 116)	Intervention groups: Different therapies based on initial response to CC. #1: CC (6.4 ± 2 months) #2: CC and hCG (4.1 ± 2.4 months) #3: hMG + hCG (4.2 ± 1.1 months) #4 hMG + hCG (4.2 ± 1.1 months) Control group: no treatment	All groups reached target tT level (600–800 ng/dl). FSH increased in all groups.	Rate of sperm in the ejaculate: Intervention group 1: 41/372 (11.0%) (*P< 0.001*) Intervention group 2: 7/62 (11.3%) (*P< 0.001*) Intervention group 3: 4/46 (8.7%) Intervention group 4: 2/16 (12.5%) (*P< 0.05*) Control group: 0/116 (0%) SSR via mTESE: Intervention group 1: 191/331 (57.7%) (*P< 0.001*)	NR	Paradoxical decrease in serum tT level on CC: 16/496 (3.2%)

					Intervention group 2: 31/55 (56.3%) (*P< 0.001*) Intervention group 3: 22/42 (52.4%) Intervention group 4: 8/14 (57.1%) (*P< 0.05*) Control group: 39/116 (33.6%)		
Song et al. (2012)	Case Series	NG NOA (n = 4) ***and*** oligospermia (n = 8)	Testosterone undecanoate 40 mg twice daily and TC 10 mg twice daily for 4 months.	Increase in FSH and LH (*p<0.01*).	Rate of sperm in the ejaculate: NOA patients: 4/4 (100%) - Max duration for sperm to return to the ejaculate: 2 months.	NR	NR
La Vignera et al. (2020) [267]	Cohort	NG NOA (n = 105) NGH NOA (n = 105)	NG: FSH 150IU 3 times a week for 3 months NGH: -Normal testicular volume: hCG 2000IU twice a week for 3 months then either FSH 150IU × 3 times a week for 3 months OR continue hCG for 3 months if low T - Low testicular volume: FSH 150IU 3 times a week and hCG 2000IU 2 times a week	NR	Rate of sperm in the ejaculate: Overall: 83/210 (39.5%) NG: 40/105 (38.1%) NGH: 43/105 (41.0%)	Pregnancy rate: Overall: 62/210 (29.5%) NG: 30/105 (28.6%) NGH: 32/105 (30.5%)	NR

SD: Standard Deviation; RCT: Randomised Control Trial; LH: Luteinising Hormone; FSH: Follicle Stimulating Hormone; tT: Serum Total Testosterone; E2: Serum Oestrogen; T:E: Testosterone Oestrogen Ratio; hCG: Human Chorionic Gonadotropin; hMG: Human Menopausal Gonadotropin; puFSH: Purified Urinary FSH; CC: Clomiphene Citrate; TC: Tamoxifen Citrate; I.M: Intramuscular Injection; S.C: Subcutaneous Injection; SSR: Successful Surgical Sperm Retrieval; FR: Fertilisation Rate; PR: Pregnancy Rate; LBR: Live Birth Rate; FR: Fertilisation Rate; mTESE: Micro-dissection Testicular Sperm Extraction; cTESE: Conventional Testicular Sperm Extraction; NG: Normogonadotropic Eugonadism; NGH: Normogonadotropic Hypogonadism; cHH: Compensated Hypergonadotropic Hypogonadism; HH: Hypergonadotropic Hypogonadism; NR: Not Reported.

Figure 1



The Hypothalamo-Pituitary-Gonadal Axis and the Causes of Male Infertility: a schematic diagram representing the hypothalamo-pituitary-gonadal axis and the hormonal signalling pathways that control the production of testosterone and spermatozoa. GnRH: Gonadotropin-Releasing Hormone; FSH: Follicle Stimulating Hormone; LH: Luteinising Hormone; ITT: Intra-Testicular Testosterone. Created with BioRender.com.

sperm production. NOA accounts for 85–90% of azoospermia cases [6]. Whilst OA is commonly treatable with surgical correction or ICSI, NOA patients require surgical testicular sperm extraction (TESE). However, both TESE and micro dissection TESE (mTESE) have success rates ranging from 30 to 64% [24]. Within this context hormone stimulation therapy has been trialled to improve sperm retrieval rates (SRRs).

The majority of the literature focusses on Azoospermia. Therefore, this narrative review will describe the contemporary data regarding the use of HST to treat NOA male infertility.

The rationale for hormone stimulation therapy

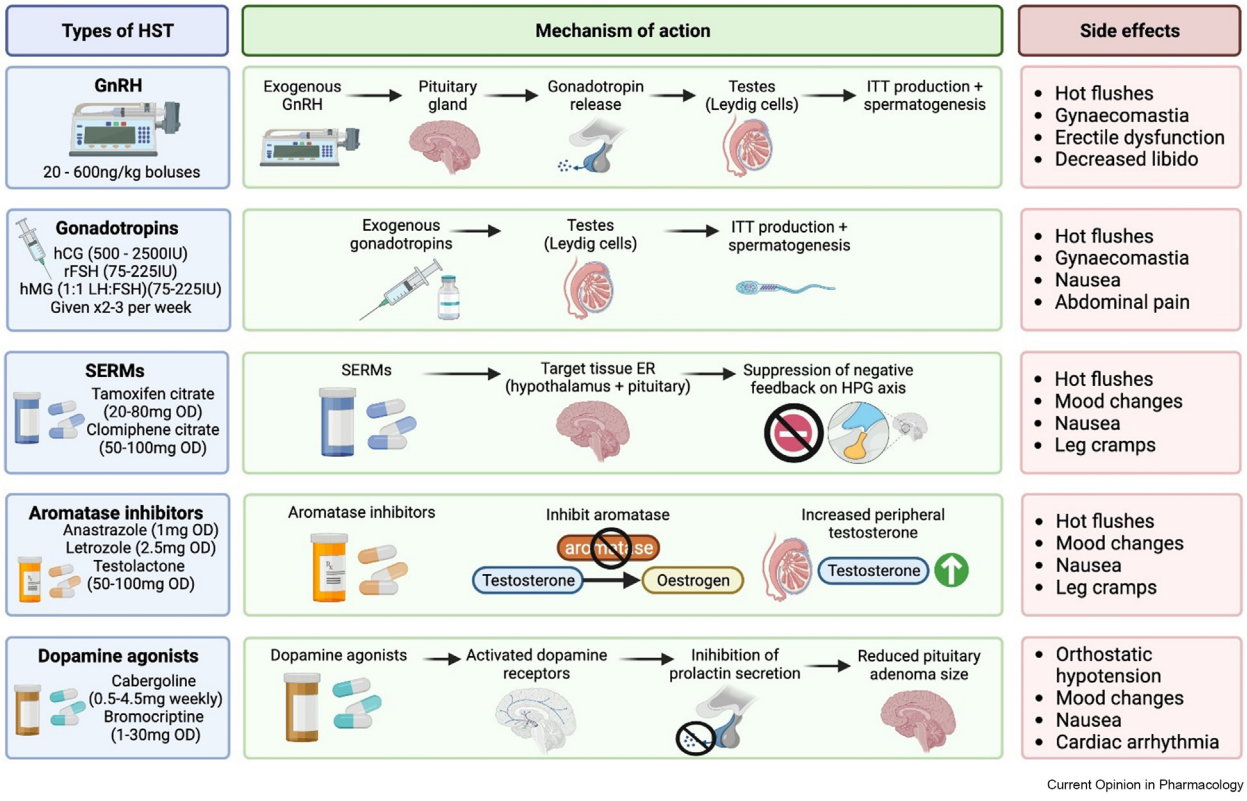
Spermatogenesis is the process by which germ cells differentiate into mature spermatozoa [25–27]. Sertoli cells control the hormonal milieu in the seminiferous tubules via follicle stimulating hormone (FSH) and nourish and protect germ cells throughout spermatogenesis [28,29]. Luteinising hormone (LH) stimulates Leydig cells to synthesise and release intratesticular testosterone (ITT) which is needed for the maturation of sperm (Spermiogenesis) [30–32].

Male hypogonadotropic hypogonadism is testicular failure secondary to gonadotropin deficiency. The rationale for HST in hypogonadotropic hypogonadism is that either replacement of the missing hormones (gonadotropin releasing hormone (GnRH) or gonadotropins) or suppression of prolactin (an inhibitory hormone) will restore the hypothalamo-pituitary-gonadal (HPG) axis. Hypogonadotropic hypogonadism represents 1.9% of azoospermia cases and 1.6% of male infertility overall [33,34].

Hypergonadotropic Hypogonadism is intrinsic testicular failure associated with gonadotropin excess. Primary testicular failure represents 75% of all male factor infertility [35]. Eugonadism describes completely normal physiological hormone levels compatible with fertility. There are several theories behind the rationale for HST in hypergonadotropic and eugonadal patients.

It has been postulated that in hypergonadotropic hypogonadism the FSH receptor has become

Figure 2



The Hormonal Treatments of Male Infertility: a diagram outlining the five main hormonal medications used to treat male infertility along with their mechanisms of action and examples of each class of medication: 1. Pulsatile GnRH; 2. Gonadotropins; 3. Selective Oestrogen Receptor Modulators; 4. Aromatase Inhibitors; 5. Dopamine Agonists. GnRH: Gonadotropin-Releasing Hormone; ITT: Intra-Testicular Testosterone; hCG: Human Chorionic Gonadotropin; rFSH: Recombinant FSH; hMG: Human Menopausal Gonadotropin; OD: Once Daily; ER: Oestrogen Receptor; HPG: Hypothalamo-pituitary-gonadal. Created with BioRender.com.

desensitised due to chronic high circulating gonadotropin levels and that hormone manipulation either with a GNRH antagonist followed by gonadotropin or through other HST may reset the HPG axis and restore spermatogenesis [36–41]. Furthermore animal and human case reports have described a testosterone independent pathway for spermatogenesis through supraphysiological HST-induced FSH stimulation [42–45]. It has been shown that ITT correlates poorly with serum testosterone (sT) [24,46–48] and therefore HST may be rationalised in eugonadism through overactivation of the HPG axis resulting in increased ITT production.

Types of hormone stimulation therapy

There have been several pharmacological therapies used to treat male infertility (Figure 2).

Gonadotropin releasing hormone

GnRH is released by the hypothalamus and stimulates pituitary gonadotropin release. In patients with GnRH deficiency, such as Kallman's syndrome, therapeutic GnRH stimulates pituitary gonadotropin secretion which subsequently induces ITT production and spermatogenesis. GnRH is mainly useful in congenital hypogonadotropic hypogonadism (CHH), excluding cases of GnRH receptor defects [49]. GnRH only exerts physiological effects when delivered in pulses [49]. Therefore, GnRH is delivered via a portable, subcutaneous pump, which administers GnRH boluses every 2 h for 12–24 months [49,50]. Doses vary from 25 to 600 ng/kg/bolus and are guided by hormonal response [49,50].

Gonadotropins

Gonadotropin therapy replicates the physiological function of LH and FSH in stimulating spermatogenesis and exists in several different formulations. Human chorionic gonadotropin (hCG) imitates LH, recombinant FSH (rFSH) imitates FSH, and human menopausal gonadotropin (hMG) contains a 1:1 ratio of LH:FSH. Gonadotropins are administered as subcutaneous injections. The typical dose of hCG ranges from

500 to 2500 International units (IU) given 2–3 times a week [49]. The typical doses of hMG or rFSH range from 75 to 225 IU given 2–3 times a week [49,51].

Selective oestrogen receptor modulators

Selective Oestrogen Receptor Modulators (SERMs) act on oestrogen receptors (ERs), in a tissue-specific manner, either as agonists or antagonists to alter the response to oestrogen [52,53]. SERMs inhibit ERs in the hypothalamus and pituitary and suppress oestrogen-mediated negative feedback on the HPG axis [52,53]. This upregulates gonadotropin and testosterone production. Tamoxifen Citrate (TC) and Clomiphene Citrate (CC) are the most commonly used SERMs. The typical doses of TC and CC range from 20 to 80 mg and 50–100 mg respectively, given once daily [51].

Aromatase inhibitors

Aromatase Inhibitors (AIs) inhibit the aromatase-mediated conversion of testosterone to oestradiol within Leydig cells [54]. This increases peripheral circulating testosterone levels and decreases peripheral circulating oestrogen levels [55]. The diminished oestrogen levels reduce oestrogen-mediated negative feedback on the HPG axis, upregulate gonadotropin production and consequently increase ITT production and spermatogenesis [55]. The common AIs include Anastrozole, Letrozole, and Testolactone. The typical doses of Anastrozole, Letrozole, and Testolactone are 1 mg, 2.5 mg, and 50–100 mg respectively, given once daily [51].

Dopamine agonists

Dopamine Agonists (DAs) activate dopamine receptors to induce the inhibition of prolactin secretion and the reduction of pituitary adenoma size [56]. By removing prolactin's inhibitory effect on the pituitary and hypothalamic hormone secretion, DAs reactivate the HPG axis [57]. DAs are therefore, used almost exclusively for hypogonadotropic hypogonadism secondary to prolactin-secreting pituitary adenomas [57]. The commonly used DAs include Cabergoline and Bromocriptine. The typical doses of Cabergoline and Bromocriptine range from 0.5 to 4.5 mg weekly and 1–30 mg daily respectively [58].

For the purposes of this review, we will describe the use of HST in hypogonadotropic hypogonadism, hypergonadotropic hypogonadism, and eugonadism.

Hormone stimulation in hypogonadotropic hypogonadism

GnRH is well established as an effective therapy in hypogonadotropic hypogonadism and the literature comprises of 15 cohort studies, 21 case series, 11 case reports, and two randomised controlled trials (RCTs) [59–108]. Studies have reported clear clinical efficacy with GnRH therapy and in the majority (65%) of studies more than 70% of subjects produced sperm in their ejaculate [59–108]. Lin et al. observed that GnRH significantly increased sperm retrieval rates compared to gonadotropins in idiopathic hypogonadotropic hypogonadism (52.99% vs 25.24% ($p < 0.05$)) [107]. Dwyer et al. reported that rFSH with GnRH increases the SRR compared to GnRH alone (100% vs 66% $p < 0.05$) [109]. However, GnRH is not commonly used in clinical practice because of the inconvenience of wearing the GnRH pump and the need to change the needles and batteries. Furthermore, there is a risk of GnRH antibody formation, particularly in cases of erratic compliance [49].

The most studied pharmacological therapy for hypogonadotropic hypogonadism is gonadotropins (4 RCTs, 50 cohort studies, 36 case series, and 28 case reports) [93–108,110–230]. Initial case studies demonstrated the restoration of spermatogenesis with hCG in hypogonadotropic hypogonadism [111–113,231]. Furthermore, it was observed that between 60 and 70 days of FSH receptor agonism is needed to stimulate spermatid production [111–113,231]. Within the literature, various drug combinations, doses and treatment durations have been reported, which makes comparison difficult [93–108,110–230]. Overall, hCG and hMG were the commonest pharmacological treatments studied [93–108,110–230]. These studies examined 4637 patients altogether, and in the majority (78%) of studies, over 70% of subjects had sperm successfully retrieved [93–108,110–230]. Zhang et al. demonstrated no significant difference in SRR outcomes between continuous and sequential gonadotropin regimes ($p = 0.397$) [197]. Bouloux et al. identified that supplementary rFSH improved SRRs compared to hCG alone (47% vs 18% $p < 0.05$) [232]. Overall, the current literature suggests gonadotropins are an efficacious treatment for hypogonadotropic hypogonadism and azoospermia. The data is somewhat limited because most studies are retrospective and have small cohort sizes.

The main data investigating the use of DA's in hypogonadotropic hypogonadism has been in participants with hyperprolactinaemia-induced hypogonadism [233,234]. Webster et al. reported that Cabergoline restored HPG axis function in 82% of 118 patients with hypogonadotropic hypogonadism, compared to 0% treated with the placebo ($p < 0.01$) [235]. Verhelst et al. confirmed that Cabergoline normalises prolactin in 70% of patients ($n = 455$) and achieved prolactin normalisation in 84% and 70% of Bromocriptine intolerant and resistant patients respectively [236]. DAs are effective in restoring HPG axis function and semen parameters in patients with hypogonadism secondary to hyperprolactinaemia [237].

There is limited data supporting the use of AI's in hypogonadotropic hypogonadism. A small number of case reports and case series suggest AIs may normalise hormone profiles in patients with hypogonadotropic hypogonadism and morbid obesity [238–249]. However, these reports mostly describe changes in hormone profiles without clinical improvements in spermatogenesis [238–249]. One un-published abstract reports successful pregnancies in 3 patients from a cohort of 12 following treatment with letrozole [246]. Whilst the data is very limited, there may be a role for AIs in hypogonadotropic hypogonadism.

Hormone stimulation in hypergonadotropic hypogonadism (Table 2)

The data investigating the use of gonadotropins is level four evidence with no randomised controlled trials and comprising of only three case-control studies and one case series. All studies utilised hCG with either rFSH, purified urinary FSH, or hMG [250–253]. The contemporary literature has conflicting results regarding the efficacy of gonadotropin treatments in stimulating spermatogenesis. The three case-control studies all reported an increased SRR but only two studies reported statistical significance ([251]: $p < 0.05$ [250],: $p = 0.006$). Hu et al. trialled non-pulsatile GnRH agonism to suppress the HPG axis before gonadotropin replacement and observed a 4% SRR compared to 0% in the control group [252]. The authors noted that 40% of patients were unable to tolerate the therapy due to androgen deprivation symptoms [252]. Overall, although the literature suggests that gonadotropins may increase SRR, the majority of the data is based on retrospective, non-randomised studies with small cohort sizes.

There has been only one case-control study investigating the use of SERMS in hypergonadotropic hypogonadism [254]. Alrabeea et al. studied the use of 3–6 months of daily CC in 122 men with NOA and hypergonadotropic hypogonadism [254]. The authors reported a higher SRR in the control group compared to the intervention cohort although this was non-significant (45.9% vs 40.5%, $p = 0.695$) [254]. Given the paucity of studies, we are unable to advocate the use of SERMs in hypergonadotropic hypogonadism.

There have been three case-series, one case-control study, and one RCT investigating the use of AIs [255–259]. All five studies reported significant increases in sT and/or testosterone: oestrogen ratio. Two case series reported SRRs of 0% [255] and 23.5% [256], whereas Shoshany et al. showed low rates of sperm in the ejaculate (0%) but higher SSRs at mTESE (72.7%) [258]. Majzoub et al. did show a non-significantly increased SSR rate at mTESE for patients taking anastrozole compared to controls (37.5% vs 0%), but statistically does not report the results of the second mixed study arm separately [259]. Cavallini et al. observed a return of sperm to the ejaculate in 100% of the intervention group compared to 0% in controls ($p < 0.05$) [257]. The data is conflicting regarding the efficacy of AIs in hypergonadotropic hypogonadism and particularly regarding whether AIs are more likely to improve rates of sperm in the ejaculate or at mTESE.

Several studies have trialled a combination of hormone stimulation therapies in infertile men with hypergonadotropic hypogonadism. Four case-control studies and one case series trialled mixed combinations of hormone therapies including hCG, rFSH, Anastrozole, Testolactone, CC and Testosterone [259–263]. All five studies reported no statistically significant increases in SSR, pregnancy, or live birth rates compared to control groups [259–263]. Furthermore, Reifschneider et al. reported a greater rate of SSR in the control group (61%) compared to the intervention group (51.1%), though this was not statistically significant [260]. The use of testosterone therapy in some cohorts may explain poor SSR rates given exogenous testosterone is known to abolish the HPG axis functionality and spermatogenesis [264–266].

Hormone stimulation in eugonadism (Table 2)

There have been four case-control studies and three case series studying the use of gonadotropins [267–273]. Three case-control studies reported an increase in sperm production in the ejaculate and SSR with gonadotropin therapy [268,272,273]. However, only two of these studies reported statistical significance [272,273]. Cocci et al. also observed a statistically significant increase in fertilisation and pregnancy rates with the use of gonadotropin therapy compared to eugonadal NOA controls (24% va 8%, $p < 0.05$) [272]. The three case series reported varied overall SSR rates of 18.1% [270], 22.4% [269] and 39.5% [267]. The heterogeneity of treatment regimens and durations mean it is difficult to make any inferences regarding the clinical efficacy of gonadotropins in eugonadal patients.

The largest study in the literature investigating SERMS in eugonadal infertile men was a case-control study, Hussein et al., that investigated the effects of CC on 496 eugonadal infertile men. The authors titrated the drug regime to target a sT between 20.8 and 27.7 nmol/L and observed an significant increase in SRR with the intervention group compared to the untreated controls (57% vs. 33.6%, $p < 0.05$) [273]. 124 patients whose sT did not increase or paradoxically decreased on CC were transferred to different study arms, yet their SSR rates were similar [273].

Only one case series examines AIs in eugonadal patients [274]. Cavallini et al. shows six months of daily Letrozole significantly increases sT, LH, and FSH, decreases oestrogen, and restores sperm to the ejaculate [274]. However, this is only in a small case series of 4 men [274]. Given the paucity of evidence, we could not recommend using AIs to treat eugonadal infertility.

Hormone stimulation in mixed cohorts

Five studies examined various HST regimens (hCG [275–277], rFSH [278], CC [277,279], and hCG with rFSH [276]) in mixed populations of hypergonadotropic and eugonadal infertile men [275–279]. One unpublished case-control study showed a statistically significant increase in SSR with 6 months of hCG treatment (66.6% vs 33.3%, $p < 0.05$) [275]. A cohort study reported that whilst 23% of their patients produced sperm in the ejaculate, a majority of their cohort did not show improved SRRs on CC (77%) [279]. The other three studies were case series that reported low SRRs of 0% [277], 19% [278], and 25% [276]. Given the variation in treatment regimens and theoretical differing rationales for HST in these groups of patients, these data do not show clear utility of HST in these patients.

Conclusion

There is an urgent need to optimise SRRs and the management of male infertility. However, the literature supporting the use of HST is limited by a lack of high-level evidence, particularly RCTs. There is a theoretical plausibility supporting the use of HST in hypogonadotropic hypogonadism and this is reflected in the literature, which is largely supportive of the role of gonadotropins in restoring spermatogenesis. However, there is conflicting data regarding the use of HST in infertile men with hypergonadotropic hypogonadism and eugonadism. A recent meta-analysis demonstrated that HST may improve SSR in eugonadism but not hypergonadotropic hypogonadism, but the evidence level was poor, and the authors recommended the use of HST only in a clinical trial setting until more RCTs are performed [51].

The European Association of Urology and the Endocrine society both state that gonadotropins should be considered the standard treatment for men with hypogonadotropic hypogonadism who desire fertility but that they do not recommend any HST for induction of fertility in primary testicular failure [6,280]. Contemporary literature also lacks objective measures of fertility including PRs and LBRs. This is important because there needs to be greater understanding regarding whether HST can change clinical outcomes. Furthermore, there needs to be an objective measure of all the potential adverse outcomes of HST. There is some data showing that HST can cause loss of libido, loss of hair, and cutaneous rashes all reported exclusively with AI use, and acne associated with gonadotropin use. There are also reports of venous-thromboembolism (VTE) in patients with Klinefelter's Syndrome on HST [281–283]. Within the context of these adverse events, HST can only be recommended for male infertility secondary to hypogonadotropic hypogonadism and further RCTs assessing PRs, LBRs and drug safety profiles are needed.

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** of outstanding interest

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