Protocol for Induction of Puberty with Gonadotropins in Adolescent Males with GnRH or Gonadotropin Deficiency

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Background Congenital hypogonadotropic hypogonadism (CHH) is an inherited condition which leads to absent, partial or arrested pubertal development in adolescence [1]. The condition may be secondary to lack of gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus or abnormal gonadotropin (luteinizing hormone, LH and follicle-stimulating hormone, FSH) secretion from the anterior pituitary gland, leading to a lack of endogenous sex steroid production from the gonads. CHH may be idiopathic or associated with anosmia, when it is termed Kallmann syndrome. It is also seen as part of a syndrome or in combination with other pituitary hormone defects.
Male patients with CHH may have micropenis and/or cryptorchidism, due to gonadotropin deficiency during foetal development and the post-natal period of mini-puberty. Other associated clinical signs, known as 'red flags' include synkinesis (mirror movements), deafness, midline defects including cleft palate and renal agenesis, and skeletal, teeth and ear anomalies. Mini-puberty provides a window of opportunity for diagnosis of this condition via endocrine investigation. Inhibin B and AMH are also useful markers of Sertoli cell function in male patients, even after mini-puberty, and inhibin B is characteristically low in patients with CHH [2]. While unmeasurable inhibin B and AMH are also seen in patients with anorchia, this will be accompanied by raised gonadotropin concentrations in these patients and thus can be distinguished from CHH. Genetic testing for deleterious variants in genes underlying CHH can also aid diagnosis.
Scope Induction of puberty in male patients with congenital hypogonadotropic hypogonadism has traditionally been with low and increasing doses of testosterone from the age of 12 years. However, whilst this management can induce virilization, it will not promote testis growth nor potential for spermatogenesis for men with this condition [3]. Particularly for those with cryptorchidism and pre-pubertal testicular volumes (<4mls), pretreatment with FSH is important to promote expansion of the Sertoli cell population [4-8]. This guideline is aimed at providing a practical protocol for paediatric endocrinologists and endocrinologists for induction of puberty in male adolescent patients with this condition.

Inclusion criteria: Male patient ≥ 12 yrs of age with *one or both*:

i) High clinical suspicion of hypogonadotropic hypogonadism by clinical and biochemical criteria [1, 2], including *at least one of*
   a. Inhibin B <65pg/ml
   b. Red flags – cryptorchidism, micropenis, synkinesis, anosmia etc.
   c. Suspicion of evolving hypogonadotropic hypogonadism with additional pituitary hormone defects (GH, TSH, ACTH deficiency)

ii) Diagnosis of hypogonadotropic hypogonadism confirmed by genetics [9]

Therapy and Monitoring in Patients with Testes Volume < 6ml*

Baseline investigations: serum (S)-LH, S-FSH, S-testosterone, S-inhibin B, Testis volume (US), Tanner stages and bone age (BA) if not done in the last 6 months.

1. rFSH 75 IU sc three times per week on Mon/Weds/Fri for 2 months

Close monitoring^ of serum FSH to ensure target levels (4-6 IU/l)
rFSH dose adjustment as needed (if serum FSH < 4 IU/L, increase incrementally up to 150 IU every other day)

After 2 months repeat the baseline investigations including testis US and start:

2. rFSH 75-150 IU sc three times weekly (to keep FSH 4-6IU/L)+ hCG 500IU sc once weekly (increased to 1000IU sc once weekly after 3 months)

Ongoing assessment and investigations: Measure peak^^ S-testosterone 3-4 weeks after starting hCG therapy. Monitoring of Tanner stages, presence of gynaecomastia, testis volume, peak S-testosterone, S-FSH, S-inhibin B and testis volumes every 3-4 months for the first 18 months. BA annually.

Individual responses to hCG vary. Dose adjustment of hCG may be needed to achieve peak testosterone (serum) in the low normal adult range (around 10nmol/L) after 6 months, and 20nmol/L after one year of start of hCG (after two years in patients <14 yrs of age)

If required, hCG dose can be increased in a stepwise fashion, to 1000IU once weekly, then to 1000IU twice weekly, and then to a maximum of 1,500 IU twice weekly.

Semen analysis: once patient is able to produce a semen sample and testicular volume >10-12ml. Early morning urine sample for spermaturia can also be checked depending on local protocols. The timeframe from start of induction to semen analysis is variable but should be completed within 3 years.

*Training and support for sub-cutaneous injections provided by endocrine CNS team.

^Monitoring of FSH initially at 14 days post starting treatment, then repeated 10-14 days after dose adjustment or at 4-6 weeks post starting treatment if no dose adjustment.
Samples to be taken pre dose.

^^Measure peak s-testosterone by taking sample 3-4 days after the hCG injection.

Therapy and Monitoring in Patients with Testes Volume ≥ 6ml†*

Baseline investigations: S-LH, S-FSH, S-testosterone, S-inhibin B, Testis volume (US), Tanner stages and BA if not done in the last 6 months.

1. hCG 500-1,000 IU sc once/twice weekly

Advise to start with the lower end of the dose range in younger patients, especially ≤13 yrs. Titrate dose based on peak^^ S-testosterone in the low normal adult range (around 10 nmol/L).

Ongoing assessment and investigations: Measure peak^^ S-testosterone 3-4 weeks after starting hCG therapy. Monitoring of Tanner stages, presence of gynaecomastia, testis volume, peak^^ S-testosterone, S-E2, S-FSH, S-inhibin B and testis volumes every 3-4 months for the first 18 months. BA annually.

Semen analysis: once patient is able to produce a semen sample and testicular volume > 10-12ml. *If no sperm production on semen analysis, no further increase in testes volume or falling inhibin B by 6-12 months change to:*

2. rFSH 75 IU sc three times per week on Mon/Weds/Fri **+** hCG 1,000 IU sc once/twice weekly

Close monitoring of S-FSH^ to ensure target levels (4-6 IU/l) with rFSH dose adjustment as needed (if S-FSH < 4 IU/L, increase incrementally up to 150 IU every other day)
Close serial monitoring of peak^^ S-testosterone.

Ongoing assessment and investigations: Monitoring of Tanner stages, presence of gynaecomastia, testis volume, peak S-testosterone, S-FSH, S-inhibin B and testis volumes every 3-4 months for the first 18 months. BA annually.

Individual responses to hCG vary. Dose adjustment of hCG to achieve peak testosterone (serum) in the low normal adult range (around 10nmol/L) after 6 months and 20nmol/L after one year of start of hCG.

If required, hCG dose can be increased to twice weekly up to 1,500 IU/dose.

Consider hCG dose reduction if gynaecomastia or excessive acne occur

Semen analysis: once patient is able to produce a semen sample and testicular volume > 10-12ml

*Training and support for sub-cutaneous injections provided by endocrine CNS team.

^Monitoring of FSH initially at 14 days post starting treatment, then repeated 10-14 days after dose adjustment or at 4-6 weeks post starting treatment if no dose adjustment. Samples to be taken pre dose.

^^Measure peak s-testosterone by taking sample 3-4 days after the hCG injection.

Special considerations

1. Testosterone naïve patients or those with early arrested puberty
   - Lower starting dose of hCG to 500 IU sc once per week for first 6 months of treatment
   - Aim for peak testosterone (serum) around 5 nmol/L in the first 6 months of treatment
   - Increase to 1000 IU once/twice per week for 2nd 6 months of treatment with aim for peak serum testosterone of 10 nmol/L

2. Testosterone pre-treatment
   - Testosterone pre-treatment is not a barrier to use of gonadotropins
   - Testosterone therapy can be continued during the use of rFSH to maintain testosterone concentrations and then discontinued when rhCG is introduced
   - Close monitoring as per the protocol above should be observed

3. Patients with hypopituitarism or reduced adult height prediction:
   - In addition to annual BA, carry out annual calculation of delta BA / delta CA ratio and adult height predictions to monitor growth through puberty [10]

†In patients with testes volumes of ≥6mls it is assumed that Sertoli cell proliferation during mini-puberty has occurred and that therefore these patients do not require FSH therapy to induce puberty. However, in some patients with testes volumes ≥6mls there may still be concerns, due to e.g. low inhibin B concentrations, about Sertoli cell number. In this case treatment with FSH is advised as for patients with testes volumes <6mls.

Medications

rFSH:

Gonal F (Merck)
Bemfola (Gedeon Richter)

rhCG:

Gonasi (IBSA)
Pregnyl (MSD, Baxter)
Ovitrelle (Merck)
Brevactid (Ferring)

All administered subcutaneously (sc)

References

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