ISRCTN39441321 https://doi.org/10.1186/ISRCTN39441321

Best practice for hormonal replacement of puberty in adolescent and young adult men with absent or incomplete puberty

Submission date
14/06/2025

Recruitment status
Recruiting

Registration date
11/08/2025

Overall study status
Ongoing

Last Edited
01/09/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Infertility affects 15% of couples. The management of male infertility is challenging, particularly in severe forms of hormone deficiency. These hormones are specific signals produced by the brain, which direct the development of the testicles or ovaries. Patients who are unable to produce these signals (named gonadotropin hormones) have a condition called gonadotropin deficiency (GD).
For adult men with GD, treatment for fertility is often unsuccessful. This is because hormones drive the development of the testicles in childhood, a vital process to enable later sperm production. Despite adult hormone replacement, individuals may suffer infertility in addition to chronic health and psychological issues.
Standard treatment for lack of puberty in adolescent males with GD is with testosterone. This helps with physical development, but not with testicular development or sperm production. PPI work with patients and carers has highlighted the importance for young men with GD of adequate pubertal development, testicular maturity and the ability to make sperm.
In contrast, puberty replacement with gonadotropin hormones enables physical maturity and a growth spurt, as well as specific testicular growth, to occur. These medications are currently used in adult patients with GD within fertility services, but can be used in puberty to allow reproductive development at the appropriate age.
This study will assess the effectiveness of gonadotropin therapy for puberty induction in young males (12-35 years) with GD. We will address the best combination of gonadotropins to help patients make sperm and the reasons for differences in response to these medications between patients. We will interview patients to understand their experiences of receiving gonadotropin therapy.

Who can participate?
Male patients aged between 12 and 35 years with gonadotropin deficiency

What does the study involve?
The Partial Treatment group will receive subcutaneous gonadotropin injections of BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per

week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months.
The Partial Control group will receive subcutaneous gonadotropin injections of hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months AND IF criteria for rescue therapy is met at 9-12 months will receive subcutaneous gonadotropin injections of recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 6-15 months.
The Severe Treatment group will receive subcutaneous gonadotropin injections of recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 2 months, followed by BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 16-22 months.
The Severe Control group will receive subcutaneous gonadotropin injections of BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months.
All groups will be followed up at 4-6 monthly study visits with clinical examination and auxology, blood tests and testicular ultrasound. Once testicular development has reached a threshold of 10-12 ml volume, semen analysis will be carried out. Pre- and post-treatment quality of life will be assessed by questionnaire and qualitative interviewing will be offered. Whole genome testing will be carried out at baseline.

What are the possible benefits and risks of participating?
There are potential benefits of participating in the study, including for physical development and well-being. Participants will receive access to treatment with gonadotropins, which results in physical development that is over and above what would occur if receiving the current NHS standard of care, namely testosterone replacement. The main visible change participants would be aware of is the growth and development of the testicles. In addition, we anticipate that receiving gonadotropin therapy in puberty will result in improved fertility and psychosexual benefits in adult life.
The medications given in this trial are provided to participants to take home and to self-administer. Usually, the young person will give themselves the subcutaneous (just under the skin) injection, or their parent or caregiver will do this for them. The injections are given with a very small and thin needle and are usually pain-free.
Risks of these medications are low, with the most frequently occurring adverse effects of mild gynaecomastia (male breast development), acne or injection site reaction experienced in 8.1%, 6% and 5% of patients, respectively, in our recent review of the published studies on the use of these treatments. This is confirmed by a review of male patients with GD from our service receiving these therapies in the past 12 months, in whom 1 in 20 have developed mild gynaecomastia, and no patients have reported other adverse effects. It is important to note that these clinical features also occur in young men undergoing spontaneous puberty or those undergoing pubertal induction with testosterone.
The protocol has been designed with input from patients and carers and with awareness of potential distress that may arise during involvement activities. The burden of activities has been minimised wherever possible and closely mirrors the standard assessments that occur in NHS practice for young people with GD. Our work with patients and the public has highlighted how motivated this patient group is to improve therapies for this underserved condition, and that families often seek out specialist clinicians who can offer gonadotropin therapy for pubertal induction, sometimes travelling across the country for treatment. However, we are also mindful of the need for sensitivity in recruiting participants to this study, to balance needs of the young person with those of their family/carers, and that a proportion of children and young people

with GD will opt to follow standard treatment protocols for GD with testosterone as these are more straightforward.
For younger participants, the acceptability of semen analysis is important to explore. The protocol for collecting semen for analysis has become more straightforward for boys and young men, with collection within the patient's home and then transfer of the sample to the lab for analysis. This is much more acceptable than the previous system of having to provide a sample at the testing centre. Our practice is to discuss the purpose and process of semen analysis from the beginning of the patient's treatment and repeat the information on a regular basis, to allow the patient to express any concerns or fears, answer questions and to ensure they are psychologically well prepared for the process once ready physically.

Where is the study run from?
Queen Mary University of London (UK)

When is the study starting and how long is it expected to run for?
June 2025 to January 2030

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
1. Dr Sasha Howard, s.howard@qmul.ac.uk
2. Shared team inbox, pingstudy@qmul.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

Contact name
Dr Sasha Howard

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1009018

Protocol serial number
CPMS 58941

Study information

Scientific Title
Pubertal induction with gonadotropin treatment in males with hypogonadotropic hypogonadism: the PinG study

Acronym
PinG

Study objectives
Objectives:
1. To compare the capacity to make sperm following treatment to replace puberty, with either a single (hCG) medication or a combination of two different medications (rFSH and hCG), in male patients who are partially affected with gonadotropin deficiency (GD).
2. To compare the capacity to make sperm following treatment to replace puberty, with or without prior treatment with rFSH, followed by a combination of two different medications (rFSH and hCG), in males who are severely affected with GD.
3. To compare further markers of success in replacement of puberty (including size of their testicles, blood markers of testicle function and quality of their sperm) in patients who are partially affected with hypogonadotropic hypogonadism (HH), who have received either a single (hCG) medication or a combination of two different medications (rFSH and hCG).
4. To compare further markers of success in replacement of puberty (including size of their testicles, blood markers of testicle function and quality of their sperm) in patients who are severely affected with HH, with or without prior treatment with rFSH, followed by a combination of two different medications (rFSH and hCG).
5. To assess differences in how well patients with HH respond to these treatments between patients who have different gene changes responsible for their condition.
6. To assess quality of life in patients with HH and their carers, before and after these treatments to replace puberty.

Ethics approval required
Ethics approval required

Ethics approval(s)

notYetSubmitted, ref: 25/LO/0504

Study design
Open randomized controlled trial

Primary study design
Interventional

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Gonadotropin deficiency secondary to hypogonadotropic hypogonadism or pituitary hormone deficiency

Interventions
The PinG study is an open-label randomised controlled study. The protocol is stratified according to disease severity, into those participants with partial congenital hypogonadotropic hypogonadism (CHH) as described according to the inclusion criteria listed and maximal testes volume ≥4 ml, and participants with severe CHH as described according to the inclusion criteria and maximal testes volume <4 ml.

Partial Treatment arm – will receive subcutaneous gonadotropin injections of BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months.

Partial Control arm - will receive subcutaneous gonadotropin injections of hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months AND IF criteria for rescue therapy is met at 9-12 months will receive subcutaneous gonadotropin injections of recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 6-15 months.

Severe Treatment arm - will receive subcutaneous gonadotropin injections of recombinant (r) FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 2 months, followed by BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 16-22 months.

Severe Control arm - will receive subcutaneous gonadotropin injections of BOTH recombinant (r) FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months.

All arms will be followed up at 4-6 monthly study visits with clinical examination and auxology, blood tests and testicular ultrasound. Once testicular development has reached a threshold of 10-12 ml volume, semen analysis will be carried out. Pre- and post-treatment quality of life will be assessed by questionnaire and qualitative interviewing will be offered. Whole genome testing will be carried out at baseline.

Within both the partial GD and severe GD groups, participants will be randomised within REDCap in a 1:1 ratio.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Follitropin alfa, chorionic gonadotropin

Primary outcome(s)
Capacity for spermatogenesis is measured by total sperm concentration ≥1 x 10e6/ml on semen analysis at 18 months of treatment

Key secondary outcome(s))
1. Testicular development measured by testicular volume via orchidometer at 0, 6, 12, 18 (+/- 24) months of treatment
2. Testicular development measured by Inhibin B concentration in blood samples at 0, 6, 12, 18 (+/- 24) months of treatment
3. Sperm quality measured by maximal sperm concentration on semen analysis at 18 (+/- 24) months of treatment
4. Treatment length to achieve spermatogenesis measured by months to reach a total sperm concentration ≥1 x 10e6/ml on semen analysis at 18 + 24 months of treatment
5. Genetic contribution to response to treatment measured by whole genome sequencing at baseline with analysis of correlation of pathogenic variants identified with primary outcomes
6. Quality of life changes after treatment measured by questionnaire at baseline and end of treatment

Completion date
31/01/2030

Eligibility

Key inclusion criteria
1. Age ≥12 and <35 years
2. Males
3. Participant or their parent/carer is willing and able to give informed consent for participation, with informed assent from the participant if <16 years
4. Able and willing to comply with all study requirements, including ability to participate in study for a minimum of 18 months
5. Willing to allow their General Practitioner (GP) to be notified of participation in the study
6. Diagnosis of gonadotropin deficiency (hypogonadotropic hypogonadism) by biochemical criteria (low or undetectable basal LH and FSH with low or undetectable testosterone)
7. Additional confirmatory features (at least one of):
7.1. Inhibin B <150 pg/ml
7.2. Red flags – small testes volumes, cryptorchidism, micropenis, synkinesis, anosmia
7.3. Clinical hypogonadotropic hypogonadism with additional pituitary hormone defects (GH, TSH, ACTH deficiency)
7.4. Peak LH on GnRH stimulation testing of <5 IU/l

7.5. Diagnosis of congenital hypogonadotropic hypogonadism confirmed by genetic testing
7.6. MRI pituitary/ olfactory bulbs demonstrating anatomical abnormalities consistent with hypogonadotropic hypogonadism
8. Patient requiring treatment to induce or complete the induction of puberty

Additional inclusion criteria for partial GD:
1. Maximal testes volumes ≥4 ml

Additional inclusion criteria for severe GD:
1. Maximal testes volumes <4 ml

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
12 years

Upper age limit
35 years

Sex
Male

Key exclusion criteria
1. Age <12 or ≥35 years
2. Females
3. Functional hypogonadism due to low caloric intake, excessive exercise or chronic disease
4. Primary hypogonadism
5. Constitutional or self-limited delayed puberty
6. Active hypothalamic or pituitary tumour
7. Uncontrolled non-gonadal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders)
8. Hypersensitivity to the active substance or excipients

Date of first enrolment
31/08/2025

Date of final enrolment
31/03/2028

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
80 Newark Street
London
United Kingdom
E1 2ES

Study participating centre
Uclh
250 Euston Road
London
United Kingdom
NW1 2PQ

Study participating centre
Great Ormond Street Hospital
Great Ormond Street
London
United Kingdom
WC1N 3JH

Study participating centre
Hammersmith Hospital
Du Cane Road
Hammersmith
London
United Kingdom
W12 0HS

Study participating centre
St Mary's Hospital
Praed Street
London
United Kingdom
W2 1NY

Study participating centre
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Birmingham Children's Hospital
Steelhouse Lane
Birmingham
United Kingdom
B4 6NW

Study participating centre
Alder Hey Hospital
E Prescot Rd
Liverpool
United Kingdom
L14 5AB

Study participating centre
Sheffield Childrens Hospital
Western Bank
Sheffield
United Kingdom
S10 2TH

Study participating centre
Royal Hospital for Children and Young People
50 Little France Crescent
Edinburgh
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EH16 4TJ

Study participating centre
Royal Hospital for Sick Children (Glasgow)
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Glasgow

United Kingdom
G51 4TF

Study participating centre
Nottingham Children's Hospital
Queen's Medical Centre
Derby Rd
Lenton
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Bristol Children's Hospital
Upper Maudlin Street
Bristol
United Kingdom
BS2 8BJ

Study participating centre
Addenbrookes
Addenbrookes Hospital
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CB2 0QQ

Study participating centre
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Study participating centre
Evelina Children's Hospital
Westminster Bridge Road
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SE1 7EH

Study participating centre
Southampton Children's Hospital
Southampton General Hospital
Tremona Road
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SO16 6YD

Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be available upon request from the study team (pingstudy@qmul.ac.uk), if the request is from teams conducting relevant research in the subject area and is deemed reasonable and appropriate by the study team. No data will be released for sharing until at least 18 months after study completion. All tagged identifier fields will be removed from the dataset prior to export and transfer to ensure that no participant identifiable data is transferred or accessed. Only data from participants who have consented to data being shared will be included (this is an optional consent on the study ICF). Deidentified study data can be shared via secure STFP transfer. Data requests will be available for a minimum of 18 months after study close.

IPD sharing plan summary

Available on request