



Growth Hormone Deficiency

A Guide for Parents and Patients



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This booklet is intended to provide help when dealing with problems or difficulties associated with your child's condition and to provide information which will enable you to understand your child's treatment better and give you a basis for discussions with your child's specialist when necessary.

If you require further general information about *growth hormone deficiency*, the Child Growth Foundation and the Growth Hormone Group are there to help you.



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PUBERTY AND THE GROWTH HORMONE DEFICIENT CHILD – Series 3 (Revised June 2000).

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The British Society for Paediatric Endocrinologists (BSPE) is an association of specialists who deal with hormone disorders in children.

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PUBERTY

Puberty is defined as the changes that take place associated with the maturation of the gonads; testes in boys and ovaries in girls. These changes include the development of secondary sexual characteristics and the pubertal growth spurt, the end result being fertility. It is brought about by changes in circulating hormones released from a gland in the base of the brain, the pituitary gland. Puberty usually commences at an average age of 11 years in girls and 12 years in boys.

In children with either isolated growth hormone deficiency (GHD) or multiple pituitary hormone deficiencies (MPHD), there can be a delay in, or complete absence of, pubertal development. An explanation of why this happens, and how it can be treated, is given in the following sections.

ISOLATED GROWTH HORMONE DEFICIENCY

About 50% of children who have 'isolated' growth hormone deficiency also have some deficiency of the hormones affecting pubertal development (gonadotrophins, see page 5). When the child is young, it is extremely difficult to determine whether these hormones are affected but there are some clues which may be seen in young boys such as a very small penis or both testes which appear not to have descended from the lower abdomen into the scrotal sac.

When a child with, what appears to be, 'isolated' growth hormone deficiency fails to commence the pubertal changes at the normal time i.e. 11 years in girls and 12 years in boys, it remains difficult to diagnose whether this is due to gonadotrophin hormone deficiency specifically or to a 'normal' but delayed puberty. It is complicated because children with isolated growth hormone deficiency tend to go into puberty later. Doctors now recognise that there are strong psychological and medical grounds for ensuring that a child commences puberty within the same age range as his or her peer group. Thus, most specialists believe that regardless of the reason, puberty should be induced if it does not occur at the normal time.

MULTIPLE PITUITARY HORMONE DEFICIENCIES (MPHD) (Pan-hypopituitarism)

As well as being growth hormone deficient, children with MPHD will almost always be gonadotrophin deficient and induction of puberty will therefore be necessary. As with

isolated growth hormone deficiency, puberty should be induced as near as possible to the time that this would occur naturally and the aim is to imitate the natural process with a gradual build-up of oestrogen (girls) and testosterone (boys). Successful treatment is available to achieve the normal changes of puberty but fertility may be more difficult to achieve and require more specialised treatment.

Children with MPHD may have the condition as a result of treatment with chemotherapy or radiation for childhood cancer or the condition may be idiopathic' (of unknown origin).

Where the condition is the result of chemotherapy or radiation treatment, hormone replacement therapy ensures that the natural changes of puberty occur. However, if damage has also occurred to the organs necessary for reproduction (ovaries and testes) the chances of fertility will be reduced or may be impossible.

Counselling

It is therefore important that children who have undergone such treatment are counselled, by a consultant, gradually from age 10 years, with longer discussions about sexual function, ejaculation, and fertility, taking place at a later date (about 14 - 16 years in girls and boys). Obviously, the timing and extent of such discussion should be tailored to individual and parental wishes.

Where children have idiopathic MPHD, the chances of fertility will vary considerably. All the hormones required for fertility can be supplemented and where the ovaries or testes have developed sufficiently to respond to hormone replacement therapy, fertility is usually possible. It is important that after growth and sexual maturation is complete, medical care is handed over to an adult reproductive endocrinologist or gynaecologist, so that a full range of treatment for induction of fertility may be offered.

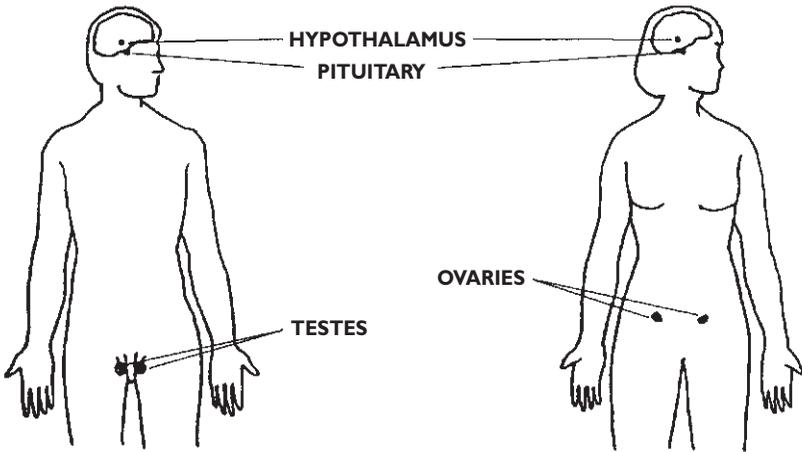
HORMONES AFFECTING PUBERTY

The brain contains two regions which produce the hormones responsible for the onset of puberty. One of these is the HYPOTHALAMUS and the other is the PITUITARY GLAND.

Puberty commences when the hypothalamus starts sending high levels of gonadotrophin releasing hormone to the pituitary gland which is then 'triggered' to start releasing higher levels of follicle stimulating hormone (FSH) and luteinising hormone (LH). These two hormones are known as the GONADOTROPHINS. When a child has gonadotrophin deficiency, or insufficiency, it is usually the result of a lack of gonadotrophin releasing hormone (GnRH) in the hypothalamus. Consequently, the pituitary gland is not stimulated to release LH and FSH in either the correct quantity or according to the normal pattern of release.

HORMONES AFFECTING PUBERTY

The hormone producing glands and their hormones



GLAND:	HYPOTHALAMUS	PITUITARY	TESTES	OVARIES
HORMONE(S):	GONADOTROPHIN RELEASING HORMONE (GnRH)	GONADOTROPHINS Luteinising hormone and Follicle stimulating hormone (LH and FSH)	TESTOSTERONE	PROGESTERONE and OESTROGEN
ACTION(S):	Stimulates the pituitary gland to produce the gonadotrophins.	LH: controls the production of testosterone from the testes in boys, and triggers ovulation and controls the menstrual cycle in girls. FSH: controls sperm production in boys and starts the ova ripening and helps control the menstrual cycle in girls.	Controls male sexual development and helps control sperm growth and function.	Act with LH and FSH to control the menstrual cycle. OESTROGEN also controls female sexual development.

The hormones FSH and LH initiate sperm production in the TESTES of a boy and egg production in the OVARIES of a girl. The testes and ovaries then start to produce high levels of their own hormones. These are the 'sex hormones' which are responsible for male and female sexual changes. The most important male sex hormone is TESTOSTERONE which causes the growth of facial and body hair, muscular development and an increase in penis size. The most important female sex hormone is OESTROGEN which brings about breast development. In addition to oestrogen, the sex steroid progesterone is also produced during egg producing menstrual cycles. [Note: Males also produce low levels of female sex hormones and females produce some male sex hormones].

TIMING AND DURATION OF PUBERTY

It is important that the changes of puberty should be brought about at the normal age, both for psychological and medical reasons. Children can suffer considerable anxiety if the normal external physical changes of puberty (and menstruation in girls) do not take place when their peers are experiencing these changes.

In normal puberty the changes take place gradually. The time scale for all the changes of puberty may be as short as 18 months or as long as 5 years. Where puberty is induced, it is important that the changes take place in a gradual manner, as naturally as possible. This means that induced puberty should take about three years to complete.

There are two aspects of delayed or absent puberty which are treated separately. The first is the development of sexual characteristics (breasts and pubic hair in girls; enlarged penis, facial and body hair and increased muscular development in boys). This can be successfully treated for all hormone deficient children. The second is fertility and this will usually be treated at a later age, and only when requested, after the induction of sexual characteristics has been completed.

INDUCTION OF SECONDARY SEXUAL CHARACTERISTICS

Puberty may be induced at the age it would normally occur, ie 11 years in girls or 12 years in boys or, at the very latest, if there are no signs of it occurring naturally by the age of 14 years in a girl or 14.5 years in a boy (the upper limits of normal). The appropriate treatments to initiate changes are testosterone for boys and oestrogen for girls.

Testosterone: Given at an initial low dose which is gradually increased as puberty progresses. It is given as a long acting (depot) intramuscular, injection every month to six weeks for 3 to 4 years. The treatment may be obtained from the GP and is administered by the practice nurse. Testosterone can be taken by mouth, but it is irregularly absorbed and so is often unreliable.

Testosterone will increase the size of the penis and will stimulate the production of body hair but will have no effect on the size of the testes.

One of the main difficulties associated with testosterone injections is that they cause a very sudden, rapid rise in the level of testosterone in the blood. This is associated with increased libido (sex drive) and frequency of erections. These increases in testosterone are followed later by decreases to levels well below normal. Such swings in testosterone levels can be very difficult to cope with, both emotionally and sexually. If you are having real problems with this, do discuss it with your specialist as he/she may be able to modify the dose to help prevent this from happening. Skin patches containing testosterone are available. The main advantage of the patches is that a more steady level of testosterone is released into the blood which should have considerable advantages for the patient.

Oestrogen: Given at a very low dose which is gradually increased as puberty progresses in order to achieve satisfactory breast development. It is given as a daily tablet for a duration of 3 to 4 years and is obtained on prescription from the GP on the advice of a specialist.

For children with isolated growth hormone deficiency and pubertal delay, treatment with oestrogen or testosterone will bring about the secondary sexual characteristics of puberty. The further changes (testicular growth in boys, menstruation in girls) will then happen naturally as the pituitary gland starts to secrete gonadotrophins.

For patients who are gonadotrophin deficient in addition to their other pituitary hormone deficiencies, continued testosterone (boys) or oestrogen (girls) therapy will be necessary to maintain sexual development and prevent osteoporosis. They will probably also require additional hormone treatment in order to become fertile.

INDUCTION OF FERTILITY

Males: In order to maintain sexual development and function, treatment with testosterone will be continued. Although testicular size remains small, sexual activity (erections and ejaculation) will occur normally. However, the ejaculate will be clear rather than milky as it comprises fluid from the prostate gland rather than fluid containing sperm from the testes.

In order to induce fertility, gonadotrophin therapy given in the form of human chorionic gonadotrophin (hCG) injections administered intramuscularly three times per week. This will stimulate the testes to grow and sperm to be produced. Alternatively, gonadotrophin releasing hormone (GnRH) treatment may be given. This is administered via a small pump, smaller than a “Walkman”, attached to a very thin needle under the skin, which releases the hormone in pulses every 90 minutes to 2 hours.

Treatment to induce fertility is given only for the period that the individual wants to be fertile, after which time it is stopped and he will return to testosterone therapy.

Females: In order to initiate the start of regular menstrual cycles (i.e. monthly bleedings from the womb), progesterone therapy is added to the ongoing oestrogen treatment. This is very important for keeping the uterus healthy (there is an increased risk of uterine cancer if long term oestrogen therapy alone is given). Also, there may be an increased risk of osteoporosis if hormone replacement is not established. Combined oestrogen/progesterone therapy is given as a daily tablet.

It is often difficult for a teenage girl who has delayed puberty and infertility to understand why she is taking a “contraceptive pill”. It is therefore important for the specialist to spend some time discussing the implications of this with the individual and what it will mean in terms of fertility and contraception. The individual patient may perceive this as a paradox of treatment. Time taken to explain the importance of inducing regular uterine bleeds, despite infertile cycles, is time well spent.

The induction of regular menstrual cycles which are egg producing is more difficult. The ovary needs to be stimulated through gonadotrophin (LH and FSH) therapy in order to cause the ova to develop. However, if this is not well monitored and controlled, it can lead to over-stimulation of the ovary (ovarian hyperstimulation) causing rapid, and dangerous, enlargement of the ovary. It can also lead to multiple pregnancies. For this reason, fertility treatment is usually managed through a specialist unit where potential problems such as these are minimised. Pulsatile GnRH administration is also effective, and entirely without the dangers of hyperstimulation, but it is more complicated to use.

GROWTH HORMONE DOSE IN PUBERTY

During normal puberty there is an increase in growth hormone secretion which is probably responsible for the growth spurt, in addition to increased sex steroid secretion. In some countries, specialists have recommended increasing the dose of growth hormone (approximately doubling the dose) during puberty in growth hormone deficient children. However, the data now available resulting from such an increased dose regimen suggest

that this may not have any advantage. Recently it has been suggested that growth hormone treatment in children with isolated growth hormone deficiency may actually shorten the duration of puberty and produce a rapid advance in bone maturation. Indeed, if these impressions are correct, doubling the dose of growth hormone during puberty may not be beneficial for final height.

The optimal dose to give during puberty is still inconclusive but studies are underway to investigate this. The most appropriate dose for your child during this period will be reviewed by your specialist.

LONG TERM FOLLOW-UP

Before the young adult leaves the care of the paediatric endocrinologist, it is important that careful counselling is given on puberty, fertility, and sexual function, and whether contraception is needed. In boys it will be necessary for a sperm count to be performed in the assessment of their fertility. However, most boys in the teenage years find it extremely difficult and embarrassing to produce a sample. Usually analysis of semen samples is left until the patient is seen in an adult clinic.

Handover to an adult endocrinologist should be arranged for the patient so that specialist advice can easily be accessed if problems should arise in adult life. MPHD patients will normally be automatically referred to an adult endocrinologist for continued monitoring and treatment after final stature has been achieved.

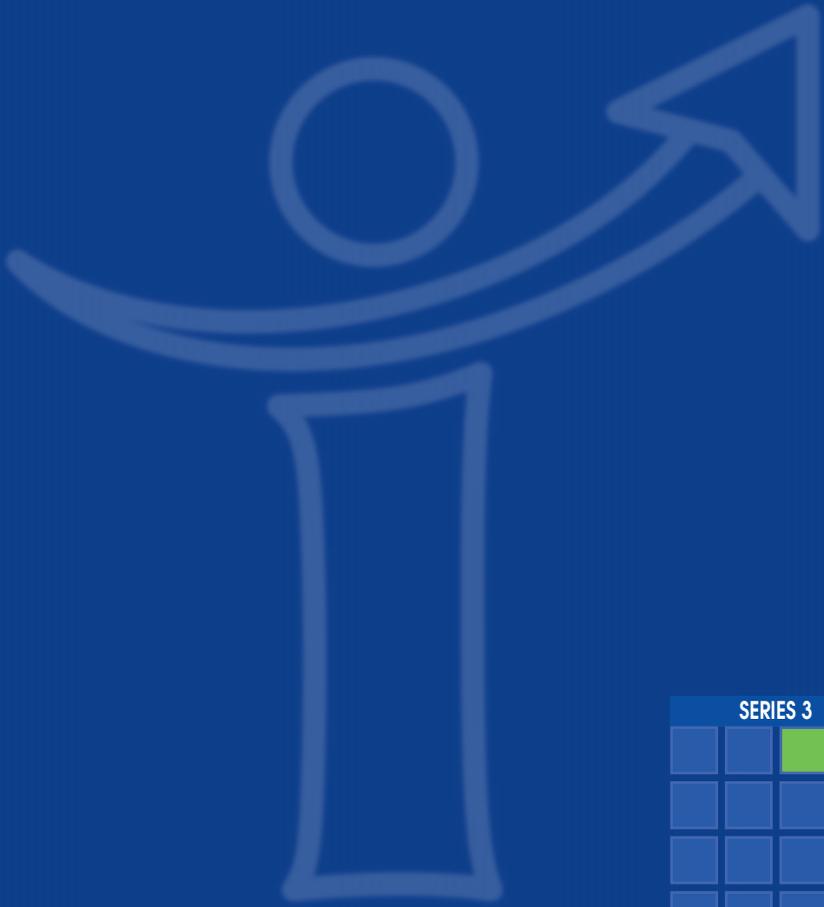
GROWTH HORMONE IN ADULTHOOD

The name of an adult endocrinologist should always be given to the young adult before leaving the care of the growth clinic and appropriate referral made for the transfer of care.

Research taking place in several different centres is being done to assess whether, for growth hormone deficient adults, there is a deterioration of wellbeing. In particular, there is strong evidence to suggest that growth hormone treatment may aid the prevention of osteoporosis (brittle bones) in adults with GHD. Trials are taking place to test bone thickness, muscle strength, stamina and the subject's own views on his/her vitality, energy and quality of life. There is also evidence that growth hormone treatment may make treatment of infertility more successful and it may be suggested, particularly in women, to return to growth hormone treatment while other treatment is given to stimulate the ovaries.

SUMMARY

The main difficulty of managing growth hormone deficiency in childhood is the assessment of gonadotrophin secretion against the natural changes of puberty. If puberty is significantly delayed, or there is doubt whether there is partial gonadotrophin deficiency, puberty should be induced. Chronic illness during childhood carries significant psychological consequences which should not be made worse by deliberately delaying the onset of puberty. The specific diagnosis and gonadotrophin status can usually be determined either during, or after, oestrogen or testosterone treatment has stopped. Growth hormone and gonadal maturation are related and the optimum dose of growth hormone to use during puberty has not yet been agreed. This shows the importance of careful clinical studies, with different doses of growth hormone, continued until final height.



SERIES 3

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