Hormones and Me

Growth Problems in Children

ANZSPED
AUSTRALIA AND NEW ZEALAND
SOCIETY FOR PAEDIATRIC
ENDOCRINOLOGY AND DIABETES

Table of Contents

About this Book

Growth Problems in Children should give you a basic understanding of the complex nature of growth and development as well as an overview of the conditions that may affect growth.

We encourage you to discuss any additional questions or areas of concern with your doctor after reading this booklet.

Merck is proud to bring you this booklet from the *Hormones and Me* educational series. We hope that you find it a valuable and helpful resource.

This booklet was reviewed and updated in 2024 by members of the Australia and New Zealand Society for Paediatric Endocrinology and Diabetes (ANZSPED, formerly APEG) Child and Adolescent Growth Subcommittee, and Professor Margaret Zacharin (Royal Children's Hospital, VIC, Australia).

Previous versions of this booklet was updated in 2019 by Prof Margaret Zacharin (Royal Children's Hospital, VIC, Australia). The 2011 version was updated with the help of Dr Tim Jones and Dr Glynis Price (Princess Margaret Hospital for Children, WA, Australia), Paediatric Endocrinologists specialising in childhood endocrine disorders and members of the Australasian Paediatric Endocrinology Group (APEG), and Dr Vinutha Shetty (Princess Margaret Hospital for Children, WA, Australia), a Paediatric Endocrine Fellow. Paediatric endocrinologists, Prof Margaret Zacharin (Royal Children's Hospital, VIC, Australia) and Dr Ann Maguire (The Children's Hospital at Westmead, NSW Australia) have reviewed the Hormones and Me series on behalf of the Australasian Paediatric Endocrine Group (APEG).

This booklet was first updated and reproduced for Australian and New Zealand readers in 2000 with the help of Dr Neville Howard (Children's Hospital Westmead, NSW, Australia). Special thanks to the original authors and editors, Dr Richard Stanhope (Great Ormond Street Hospital for Children and the Middlesex Hospital, UK), Mrs Rosemary Cordell (Child Growth Foundation, UK) and the British Society of Paediatric Endocrinology (BSPE).

Introduction

Growth is the defining characteristic of childhood. Normal growth during childhood depends on a combination of good general health, adequate nutrition, and genetics. It is important to remember that there is a wide range of what is considered ‘normal’ in how children grow and develop. Growing, like learning, does not always follow an even course and can occur in spurts.

Although most children who are below or above average size are otherwise normal, there are some important underlying conditions that can cause abnormal growth. These include gene and chromosome abnormalities (genetic disorders), endocrine gland disorders (hormonal abnormalities), cartilage or bone disorders and general chronic disease. Early detection and treatment of underlying conditions with or without growth supplements can enable many children experiencing abnormal growth to reach their potential.

“Growing, like learning, does not always follow an even course and can occur in spurts.”

Normal Growth

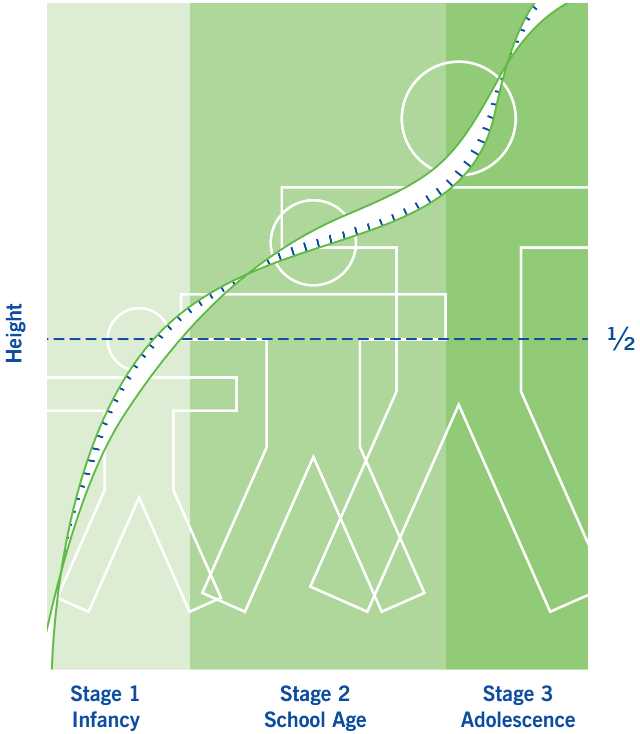
Phases of Growth

Children grow through three phases as can be seen in Diagram 1. Each has a characteristic pattern, and each is controlled by a different set of internal mechanisms.

The first phase is from birth through infancy to the pre-school years. This phase is characterised by a rapid growth of all parts of the body including the brain and the nervous system. During this time, the rate of growth steadily decreases so that the fastest speed of growth is at the beginning of this phase in the first three months of life. Hence a newborn baby is growing faster than at any other time in childhood or adolescence, and illness can severely disrupt growth potential during these early months. A number of hormones control this growth phase – thyroid hormone and growth hormone are essential for this phase of growth and development to be completed.

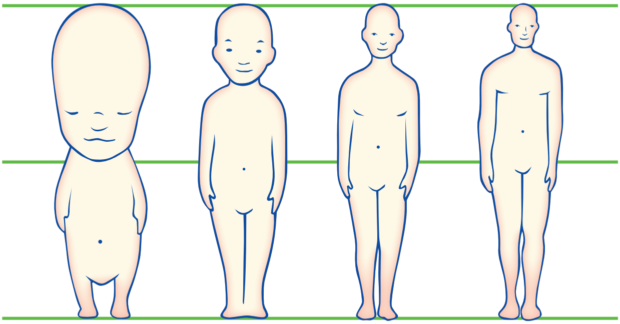
The second phase extends through the school ages until adolescence begins. The growth rate during this time is fairly steady at about 5 cm per year. Most of the growth is in the limbs so that the mid-point of the child moves upwards as can be seen in Diagram 2. In this phase, growth hormone is the most important factor controlling growth and development.

Diagram 1 : PHASES OF GROWTH



The third phase is the most complicated and stretches through adolescence (puberty) until the growth plates close over and adult height is reached. During this phase, the speed of growth picks up rapidly and then falls away to nothing (the growth spurt of adolescence). The sex hormones (testosterone and oestrogen), are the major factors controlling this phase, but growth hormone is also important. Girls usually attain pubertal growth spurt at a younger age than boys.

Diagram 2 : NORMAL GROWTH



The Essentials of Normal Growth

Children grow best when their health, both physical and psychological are optimum. Most important is the provision of adequate nutrition both in quantity and quality so that the energy needs and the specific nutrients required for growth are provided. Protection from preventable illness is also important (e.g. immunisation against common infectious diseases).

The reasons that our ancestors were shorter than current generations, relates mostly to the lack of a diet optimal for growth in their time.

Assessment of Growth

Every child should be measured regularly. If there are any concerns regarding any child’s growth, these should be discussed with the local doctor. The doctor will ask about the child’s birth, development and general health, examine the child and may order specific tests to assess the child’s growth (*see Table 1*).

> “Every child should be measured regularly.”

The measurements taken will depend on the age of the child. Weight, length and head circumference should be measured regularly in infancy. Standing height of the child without shoes is useful from two years of age and should be measured at least every year. If the growth pattern is abnormal, measurements as often as three monthly will give a more accurate view of the pattern and allow the speed of growth to be calculated. The heights of both parents should be accurately measured as these can be used to estimate the familial adult height potential of children.

Without an understanding of the height expectation in a family, it is not possible to accurately assess the size and growth potential of a child.

Assessment of Abnormal Growth

Table 1 : DETAILED MEDICAL HISTORY

General Examinations

- measurement of length, height, weight and head circumference
- body proportions, usual physical features, pubertal status
- general health
- height of parents

Screening Investigations

Blood Tests

- full blood count, markers of inflammation such as ESR
- blood chemistry (creatinine, electrolytes, calcium, phosphate)
- coeliac screen
- hormone function (e.g. thyroid hormone levels, IGF1)
- chromosome studies

Urine Tests

- microscopic examination
- chemical assessment

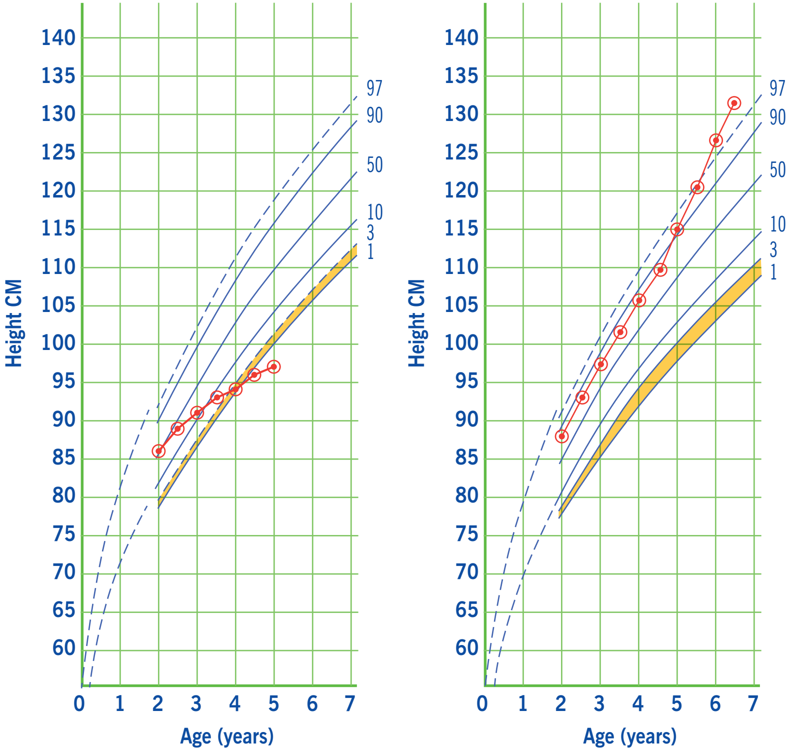
Imaging

- X-rays to assess bone structure and maturity

Centile Charts

Centile charts are graphs that show the average pattern of growth during childhood. Measurements of height (or length in infants), weight and head circumference should be plotted throughout childhood on the centile chart appropriate for the age and sex of the child. A series of measurements demonstrating the trend in growth is more valuable than one single measurement. The child’s growth should usually follow the curve of the centile graph (*see Diagram 1*). Crossing centile lines is a warning sign of abnormal growth (*see Diagram 3*).

Diagram 3 : CENTILE CHARTS



A boy’s growth chart with an example of short stature and abnormal growth

A girl’s growth chart with an example of tall stature and excessive growth

Table 2

Causes Of Short Stature	Causes Of Tall Stature And Rapid Growth
• Genetic or familial short stature • Constitutional delay in growth and puberty • Small for gestational age (SGA) / Intrauterine growth retardation (IUGR) - Placental failure - Drugs and infections - Various syndromes (e.g. Russell Silver) • Bone abnormalities (e.g. Achondroplasia) • Genetic - Chromosomal (e.g. Turner Syndrome) - Other genetic problems (e.g. Prader-Willi Syndrome) • Poor nutrition - Poor intake - Poor absorption of food (e.g. Coeliac Disease) • Chronic Systemic illness - evident (e.g. asthma) - hidden (e.g. inflammation of the bowel) • Hormone problems - Growth hormone deficiency - Other hormone deficiencies • Unexplained	• Genetic or familial tall stature - Chromosomal abnormalities (e.g. Klinefelter Syndrome) - Single gene mutations (e.g. Marfan Syndrome) • Other syndromes (e.g. Sotos Syndrome) • Hormone problems - early puberty - growth hormone excess - thyroid hormone excess • Over nutrition • Unexplained

Short Stature

Short stature – defined as having a height below the 3rd centile for age and sex – is a common problem affecting up to 3 children out of every 100. Although this may be the normal pattern of growth for an individual child, underlying causes of poor growth should be considered. The process of growth is dependent on genetics, adequate nutrition, normal bone structure and biochemistry, normal thyroxine, growth hormone and other hormones as well as general health. Disruption of normal growth may therefore be an indication of many abnormal conditions (*see Table 2*). The following sections will look at the major causes of short stature in childhood.

Familial Short Stature

The growth of a child usually reflects the size of the parents except in circumstances where parents have not realized their full growth potential due to adverse childhood nutrition. Parents who are short usually have children whose height is in the lower range of normal. Conversely tall parents usually have children who are tall. As a general rule, a child's potential adult height is the average of the parent's heights with a correction for the parent of the opposite sex to the child. See Table 3 for a formula to calculate a child's potential height.

Table 3

To calculate the potential height of a boy, the mother’s height is given an additional 13cm and averaged with the father’s height. This mid parental or “target height” can be plotted on a growth chart to estimate the centile the boy should grow along.

e.g. FATHER 180cm
MOTHER 157cm +13cm =170cm
AVERAGE 175cm = potential height =50th height centile
(*See Diagram 3*)

To estimate a girl’s height, subtract 13cm from the father’s height and follow the same steps as above.

Constitutional Short Stature with Slowed Maturation

Constitutional delay of growth is the most common cause of short stature in childhood. This is a variant of normal and is usually associated with a delay in maturation and with late puberty. Constitutional short stature often runs in families and members of the family may have a history of being ‘late bloomers’ with regard to growth and puberty.

Children with constitutional short stature usually have normal weight and length at birth. Between 6 and 30 months of age, their growth slows down and often falls below the 3rd centile line. After this dip, growth returns to normal and they remain parallel to, but below the 3rd centile line on their growth chart. Intellectual development remains normal for age. Assessment of bone maturity on X-ray will show that the bones are behind the child’s age in skeletal maturation.

This may especially be an issue around the time of adolescence. While the child's friends experience the onset of puberty and its associated growth spurt, the child with constitutional short stature will fall further behind his or her peers in growth. This child will eventually enter puberty normally and given time, children with constitutional short stature usually reach their genetic height potential. Reassurance and open communication can help deal with the emotional stress of being small.

If reassurance is not enough, there are treatments available. If lack of pubertal development is the major concern, hormone therapy with a male hormone (testosterone) in boys or female hormones (oestrogen) in girls, can initiate puberty. These forms of therapy require careful monitoring by a paediatric endocrinologist.

Genetic Disorders Causing Short Stature

Human height and growth are called complex traits as they result from a combination of many genetic (inherited from our parents) influences as well as environmental factors. Approximately 80% of the differences we see in people's height is due to genetic differences and 20% is due to differences in environmental factors such as nutrition. Most of the genetic variation in height is due to differences seen in about 9900 different genes. These genetic differences are quite common and equate to small individual effects that add together. This is why, as children inherit their genes from their biologic parents, they usually grow to be around the same height centile as their mid parental expectation. There are, however, some rare single gene differences, called mutations, that have large effects on height, causing the child to be shorter, or taller, than expected. Usually, such mutations also cause other physical health-related changes, and the resulting condition is called a syndrome.

Genes are linked together in long structures called chromosomes. and sometimes height is affected by abnormalities in the number or structure of whole chromosomes.

Turner Syndrome

Turner Syndrome is one of the most common genetic (chromosome) abnormalities in girls, affecting 1 in every 2500 live-born girls. It is caused by an abnormality of the sex chromosomes so that one of the pairs of X chromosomes found in women is partly or completely missing in some or all cells. This results in short stature and problems with ovarian development. Some affected girls have other physical features. Any girl with short stature should have a chromosome study done to test for Turner Syndrome.

> “Any girl with short stature should have a chromosome study done for Turner Syndrome.”

Girls with Turner Syndrome benefit from growth hormone treatment starting as early as possible and later usually need hormone replacement therapy (HRT) with female hormones to complete their sexual development. They will need assessment by other specialists to exclude problems that can be associated with Turner Syndrome, such as problems with their heart, kidneys and hearing.

Noonan Syndrome

Noonan syndrome affects around 1 in 1000 to 2500 babies born. It affects both girls and boys and often runs in families. A mutation in any one of 13 different genes may cause Noonan Syndrome though one in particular, called PTPN11, is responsible for 50% of cases.

Children with Noonan Syndrome have characteristic facial and body features, poor growth, sometimes a delay in adolescence and often abnormalities of the heart chambers or valves. All children with Noonan Syndrome should see a children’s cardiologist for heart investigations.

Although children with Noonan Syndrome may have normal weight and length at birth, their growth rate and final height is often less than expected. Special height charts are available for children with Noonan Syndrome and from this a paediatric endocrinologist will be able to estimate the child’s final height. Growth hormone treatment may improve adult height in some children with Noonan Syndrome but usually the growth response is not as good as other conditions such as growth hormone deficiency. Almost all children with Noonan syndrome go through puberty independent of need for sex hormone replacement, except for some boys who have had a history of undescended testes. All need assessment to ensure normal pubertal progress.

Down Syndrome

Down Syndrome (Trisomy 21) is one of the most common chromosome abnormalities affecting around 1 in 1000 babies born worldwide – male and female alike. Down Syndrome is the result of having 3 instead of 2 chromosomes number 21, an abnormality which occurs at the moment of conception.

Children with Down Syndrome have a variety of features affecting various body systems and have a characteristic facial appearance. They experience poor growth and special growth charts are available for children with this syndrome. The growth problem in this syndrome can sometimes be worsened by an underactive thyroid gland or by problems with the pituitary gland. Children who grow poorly on the Down Syndrome centile charts need investigation by a paediatric endocrinologist to identify their hormone deficiencies. Growth hormone treatment is generally not recommended.

Prader-Willi Syndrome

This condition is mostly due to inherited issues in the mothers or the father’s genes. The common problems of Prader- Willi syndrome are increased appetite, obesity, behaviour problems, short stature, sleep apnoeas, hormonal problems, scoliosis, inability to vomit and high pain threshold. Growth hormone treatment is mainly to improve body composition and improve linear growth. Sleep apnoea must be treated or excluded before starting growth hormone and a repeat sleep study is mandatory within 6 to 8 weeks after commencement of growth hormone therapy.

Other Genetic Causes

There are many other syndromes and recognisable patterns of growth that are rare and have a genetic basis. These conditions can be recognised by a paediatric endocrinologist or specialist in human genetics. Often there are specific tests to confirm the doctor's suspicions of the diagnosis. Growth patterns in this group of disorders vary widely but the diagnosis can be most useful in predicting the outcome for the individual child. Some of these conditions can benefit from growth hormone treatment.

Growth failure at birth

Small for Gestational Age (SGA) / Intrauterine Growth Retardation IUGR)

“Small for Gestational Age” (SGA) is a term used for babies whose weight and /or length at birth, is less than expected (compared with appropriate population standards for both gender and gestation), regardless of the cause. It refers to the size at birth, irrespective of the growth rate within the womb. For a baby born at full term, this is less than 45 cm long and less than 2.5 kilograms weight. Tables of length and weight are available for premature babies. Low birth length is a stronger predictor of subsequent short stature than weight.

Intrauterine growth retardation (IUGR) is a term used when babies do not grow at a normal rate within the womb and hence are born with a weight and length that are inappropriately low for the duration of pregnancy. Small for gestational age does not necessarily equate with intrauterine growth restriction. SGA includes babies with constitutional smallness or “small normal” babies who have not experienced IUGR. As small maternal size is a factor in maternal constraint, smaller women tend to deliver smaller babies.

The growth of a baby within the womb depends on maternal health and nutrition, the placenta that supplies food and oxygen to the foetus and the genetic information stored within the baby’s cells. Sometimes the cause of SGA/IUGR remains a mystery, however there are some conditions in the mother that are commonly linked to poor foetal growth. These include high blood pressure, diabetes mellitus, or infections during pregnancy, smoking and the abuse of alcohol or other drugs. Babies with genetic or chromosomal abnormalities often have SGA/IUGR. Recent evidence suggests that changes can be made after conception, depending on maternal health, that may influence foetal growth and outcome (called epigenetic programming).

Most babies born with SGA/IUGR show catch-up growth over the first two or three years of life, however in around one third of cases this does not occur. The majority of premature infants born at less than 32 weeks will show growth failure with a severity related to the degree of prematurity and the presence of chronic lung disease. There is catchup of length and weight in the majority by 5 years of age. Children who do not experience this catch-up growth may benefit from growth hormone therapy to help them reach their genetic height potential.

Russell Silver Syndrome

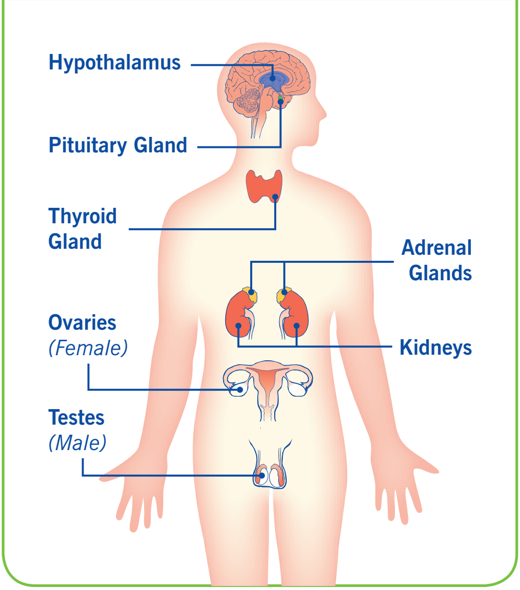
Russell Silver Syndrome describes a group of children born SGA and associated with IUGR, who display a number of specific physical characteristics as well as poor growth. These children tend to be small and thin with triangular faces, prominent foreheads and small chins. Often the limbs are of different lengths and the fifth fingers are very small. There are many other physical traits associated with this syndrome and the number of characteristics varies from child to child. Several genes associated with this condition have now been identified. Most cases of Russell Silver Syndrome are sporadic, which means they occur in people with no history of the disorder in their family. However sometimes Russell Silver Syndrome does run in families and can occur again in the next pregnancy. Assisted pregnancy is thought to be associated with this syndrome.

Most children with Russell Silver Syndrome develop normally except in size. They tend to put on weight in late childhood and experience normal puberty although puberty often occurs earlier than in their peers. Improved care including the prevention of low blood sugar levels, nutritional supplements during childhood and growth hormone therapy will help children with Russell Silver Syndrome reach their full potential. Growth hormone therapy may improve short and long term growth in this syndrome.

Hormone Disorders

Not only does normal growth depend on good health and nutrition, but also on normal secretion of growth stimulating hormones from endocrine glands. The two most important hormones required for growth are growth hormone and thyroid hormone. A deficiency in one or both of these hormones will result in poor growth and short stature. The main hormone disorders causing short stature in children are Growth hormone deficiency, Pituitary gland failure, Hypothyroidism, and Cushing's syndrome, which will be described in the following section.

Diagram 4 : THE HUMAN BODY



Growth Hormone Deficiency

Growth hormone deficiency is estimated to affect 1 child out of 5000 and is more commonly recognised in boys. It occurs when the pituitary gland at the base of the brain fails to produce adequate levels of growth hormone. The pituitary gland releases growth hormone (as well as many other hormones) in response to chemical messages from the hypothalamus, the part of the brain to which it is connected (*see Diagram 4*).

Low levels of growth hormone may be due to a problem within the hypothalamus, the link between the hypothalamus and the pituitary gland or within the pituitary gland itself.

Growth hormone is released by the pituitary gland in spurts over a 24 hour period, mostly at night during sleep and after exercise. Once released into the blood stream, growth hormone acts on the liver, kidneys and other tissues including bones to produce other chemicals known as insulin-like growth factors (IGF). These IGFs act with growth hormone to promote growth. As well as promoting growth, growth hormone has an important role in the metabolism of fat and carbohydrate and helps to maintain blood sugar levels.

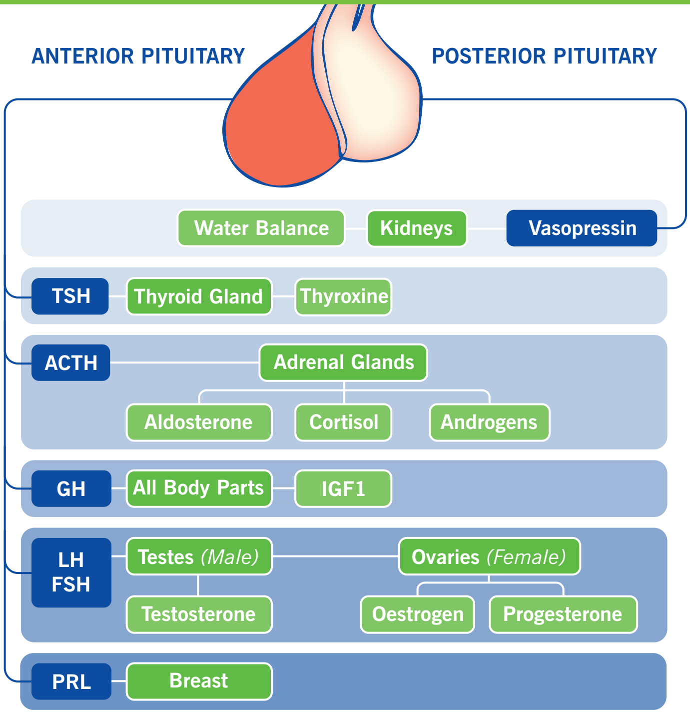
Causes of Growth Hormone Deficiency

It is not always possible to determine the exact cause of growth hormone deficiency. There may have been damage to the pituitary gland or its connections at birth or it can occur following a head injury or infection. When the cause is unknown the term idiopathic growth hormone deficiency is used.

Other causes of growth hormone deficiency include problems with the development of the pituitary gland or the hypothalamus. Sometimes growth hormone deficiency may be inherited or linked to a genetic syndrome. In some cases, damage to the pituitary gland or hypothalamus is caused by trauma, a brain tumour, surgery or radiotherapy used to treat brain tumours and leukaemia.

It is rare for children to have a complete lack of growth hormone. In most cases there is some growth hormone present but this is insufficient to maintain normal growth.

Diagram 5 : PITUITARY GLAND, HORMONES AND DEFINITIONS



TSH	Thyroid Stimulating Hormone	**LH**	Luteinising Hormone
ACTH	Adrenocorticotrophic Hormone	**FSH**	Follicle Stimulating Hormone
GH	Growth Hormone	**PRL**	Prolactin
IGF1	Insulin Growth Factor 1		

How is Growth Hormone Deficiency Diagnosed?

Children with growth hormone deficiency are small compared to other children of their age and their growth rate is poor, so they fall behind their peers (*see Diagram* 3). They tend to be chubby and to have young looking faces due to delayed bone development in the skull as well as in the limb bones.

Any child with suspected growth hormone deficiency should be assessed by a paediatric endocrinologist. This growth specialist will take medical history, details of the child’s conception, birth, development and general health. It is important to provide as many measurements of the child’s height and weight as possible so a detailed growth chart can be plotted.

A thorough physical examination of the child including accurate measurement of height, weight and body proportions will be performed. X-rays of the child’s left hand will be taken to determine maturation of the skeleton. Blood tests will be taken to look for levels of other pituitary hormones, which may also be low. These include thyroid stimulating hormone (TSH) and thyroxine (thyroid hormone levels), the sex hormone stimulating hormones (FSH and LH) and the adrenal stimulating hormone (ACTH), and insulin like growth factors (IGF1), (*see Diagram* 5).

As the blood level of growth hormone fluctuates widely over a 24 hour period it is not reliably measured in a single blood test, rather blood must be taken during a growth hormone surge or at frequent intervals over a period of time. The specialist may recommend provocation or stimulation tests, which will involve a day stay in hospital, or an overnight stay with growth hormone levels measured frequently during sleep. A specialist may decide to prescribe a short course of sex steroid (oestrogen or testosterone) before the stimulation test for older children. This is because sex hormone priming has been shown to have more accurate growth hormone response in stimulation tests. In growth hormone deficiency, there will be a lack of growth hormone production in response to two stimulation tests or inadequate peaks of growth hormone production during sleep.

Growth Hormone Treatment

Growth hormone has been used for many years with great success in the treatment of children with short stature for various reasons. In Australia, growth hormone treatment is available for children with growth hormone deficiency. However in growth hormone sufficient children, to qualify for growth hormone treatment, a child's height has to be at or below the 1st percentile for age and sex, and growth rate less than 25th percentile for bone age. Specific details of eligibility vary from time to time and need to be advised by your endocrinologist. Biosynthetic growth hormone has a small risk of side-effects which will be fully discussed with you by your doctor before commencing growth hormone treatment.

> "Growth hormone has been used for many years with great success in the treatment of children with growth hormone deficiency"

The aims of treatment are two-fold: firstly to catch up height to the normal range and secondly to increase final height. Provided treatment with growth hormone is started at a reasonably early age (before age 6 years old) both aims can usually be achieved. Later, treatment before puberty is still appropriate but the results are usually less satisfying than when treatment is started early.

The dosage of growth hormone varies according to the child's weight or body surface area and will increase as he or she grows. It is given by an injection once daily or in long acting growth hormone weekly to bi-weekly, just under the skin using a syringe or special pen with a fine needle. The injection is best given before bedtime to mimic the natural production of growth hormone as closely as possible, particularly with daily injections.

Refer to page 39 for further information on growth hormone treatment.

Pituitary Gland Failure (Hypopituitarism)

Around half of all children with growth hormone deficiency will also have some deficiency of the hormones involved in sexual development and will need treatment with sex hormones to initiate puberty. Children with deficiencies of multiple pituitary hormones will need additional treatment such as sex hormone to experience normal puberty, thyroid hormone (thyroxine) for metabolism, hydrocortisone for adrenal gland failure and often vasopressin (DDAVP) to balance water loss.

Hypothyroidism

Hypothyroidism is caused by a deficiency of the hormones produced by the thyroid gland – thyroxine (T4) and triiodothyronine (T3). These hormones are essential for normal growth and cell function. A deficiency may be present from birth and the main problem may either be the thyroid gland itself or in the hypothalamus or pituitary gland, which are responsible for stimulating the thyroid gland. A routine blood test for hypothyroidism is performed on every newborn baby to ensure early diagnosis and treatment but children may develop a thyroid problem later. This test measures TSH, and is a good test for detecting problems with the thyroid gland. However, this test will not detect central hypothyroidism (hypothyroidism associated with pituitary gland or hypothalamic problems). Therefore a normal newborn screening test does not exclude central hypothyroidism.

Later in childhood, hypothyroidism is usually caused by an abnormality of the immune system that results in damage of the thyroid gland. Sometimes hypothyroidism is due to failure of the pituitary gland to secrete thyroid stimulating hormone (TSH), (*see diagram 5*). Low levels of thyroid hormones in hypothyroidism result in slowing down of growth during childhood resulting in short stature. Other general symptoms of hypothyroidism include tiredness, constipation, dry skin and intolerance to cold. Treatment with oral thyroid hormone (thyroxine) restores normal thyroid function and normal growth.

Cushing Syndrome

Cushing Syndrome is a condition caused by overproduction of the hormone cortisol occurring either from the pituitary gland or from an adrenal gland or the prescription of large amounts of this hormone or others like it, e.g. hydrocortisone and prednisone, in conditions where steroids are essential for maintaining health. Conditions such as asthma, inflammatory bowel diseases and rheumatoid arthritis are examples. Cortisol is normally produced by the adrenal glands (located on top of the kidneys) and is vital in the regulation of blood pressure, the immune system, metabolism and growth.

Children with too much cortisol will tend to be overweight, (especially around the face and trunk), have high blood pressure and experience poor growth. They may also develop excess body hair, greasy scalp hair and acne. The condition is diagnosed by measurement of cortisol levels in the blood and urine. Treatment depends on locating the source of the over-activity and removing it. Following this, supplements of adrenal or pituitary hormones may be necessary. Growth in these children then usually resumes but growth hormone treatment is required.

In asthma and other medical conditions treated with long-term steroids such as prednisone, growth failure may occur. The physician will attempt to reduce the steroid prescribed, to improve growth. Some children however, cannot reduce their steroid due to the need for ongoing maintenance treatment of their underlying condition. Growth hormone treatment is sometimes used to improve growth, but may not be successful when the child is using steroids.

Cartilage and Bone Disorders

There are many cartilage and bone disorders which affect growth. Most of the conditions are rare and many are inherited. They are known as skeletal dysplasias. In general, body dimensions are abnormal in these disorders, with relatively short limbs. There is a spectrum of severity of relatively common short limbed dwarfing disorders from the severe Achondroplasia to the milder Hypochondroplasia. The incidence of this group of disorders is around 1 in every 15,000 babies born.

Achondroplasia

This is the most common type of skeletal dysplasia recognisable at birth. Achondroplasia is due to an abnormality of a single gene, which can occur spontaneously when a baby is conceived or be inherited from a parent with achondroplasia. This inheritance of achondroplasia is autosomal dominant, meaning a person with achondroplasia has a 50% chance of passing the defective gene to their child. If the child inherits the gene he or she will have achondroplasia. When a child with this problem is born to normal stature parents a mutation has generally occurred to cause the genetic abnormality.

Children with achondroplasia share many distinctive features including very short arms and legs, normal back length, a large head and characteristic face. Achondroplasia does not affect intelligence.

Recent discovery of a medication (“Vosoritide”) is quite promising in improving height and height velocity for pre-pubertal children with Achondroplasia and is available in Australia if certain criteria are met. Children with Achondroplasia can also have operations to lengthen bones of the arms and legs that can be successful to and improve height. Growth hormone treatment can be used in the short-term by increasing the rate of growth but has not been shown to increase final height. Its use may worsen stability of the upper spine. Specialist consultation should be undertaken if growth hormone is to be considered for these children. The best outlook for final height is likely to be achieved by combination of new medications as they become more widely available and surgery to lengthen limbs.

Hypochrondroplasia

Hypochondroplasia is another common skeletal dysplasia in which the limbs are less shortened then in achondroplasia. Recognition comes not at birth but from the doctor’s measurement of limb length and characteristic X-rays.

Final adult height in this condition is generally less than expected in the family. In the short-term, growth hormone treatment improves height but whether final (adult) height is improved is controversial.

Other Skeletal Dysplasias

There are many rare conditions of cartilage and bone development which lead to short stature and poor growth. The particular features can be recognised by paediatric endocrinologists and X-rays are used to more clearly define the diagnosis. Some of the conditions (e.g. hypophosphataemic rickets) respond to chemical treatments. Others do not respond to treatment and the use of growth hormone treatment in this group is of controversial value.

Growth Disorders Secondary to Systemic Diseases

Disorders affecting specific systems like the gastrointestinal tract, heart, lungs, kidneys and blood can affect growth. Often the diagnosis is made before the short stature is noted, but even in the asymptomatic short child, it is important to rule out hidden disorders. The following section will describe the common systemic disorders causing short stature.

Disorders of Food Absorption

Any condition that impairs the ability to absorb food resulting in poor nutrition can cause inadequate growth. Food provides the energy source for growth and the specific chemicals that are the building blocks of growth. Coeliac disease and Crohn's disease are two most likely conditions causing short stature due to poor nutrition resulting from poor absorption of food.

There are a number of other gut problems in this category, but unlike coeliac disease and Crohn's disease, the symptoms of the problem will be very obvious. Hence coeliac disease and Crohn's disease are more likely to show up as a child with poor growth.

> "Coeliac disease and Crohn's disease are two of the most common conditions causing short stature due to poor nutrition."

Coeliac Disease

Children with coeliac disease are sensitive to a protein called gluten, which is present in many grains including wheat foods. The gluten damages the delicate lining of the small bowel making it unable to absorb vital nutrients. As well as experiencing poor growth, children with coeliac disease can become very malnourished and develop gut symptoms.

Coeliac disease is diagnosed by a blood test measuring specific antibodies followed by a biopsy of the small intestine which can be done using an endoscope. Once diagnosed, it is important to eliminate gluten from the diet. Growth returns to normal with a new diet. Advice about gluten-free eating is available from the Coeliac Society of Australia.

Crohn's Disease

Poor growth is usually present in children with Crohn's disease. It involves long-term inflammation of the bowel wall, which leads to poor absorption of nutrients and there are usually gut symptoms. Inflammation can usually be well controlled with medication and a gastroenterologist should supervise management. Occasionally, surgery is required. Growth returns to normal if the poor absorption can be effectively controlled.

General Chronic Disease

Almost all chronic disease in childhood can cause short stature for reasons that are not always clear. Some of the conditions in which poor growth can occur are listed in table 4. Sometimes it is the treatment as well as the disease itself that interferes with normal growth. Long-term therapy with prednisone and other steroids, which are used to control inflammation in many chronic diseases (e.g. asthma), can result in growth disorders. (*See Cushing Syndrome page 28*).

> "Almost all chronic disease in childhood can cause short stature for reasons that are not always clear"

Anorexia nervosa, a common eating disorder, most frequently seen in adolescent girls, can be associated with serious growth failure – partly due to poor growth secondary to lack of nutrition, and partly due to failure to start or continue with puberty.

Table 4 : CONDITIONS OF CHRONIC ILLNESS ASSOCIATED WITH POOR GROWTH

- Anaemias & other blood disorders
- Malnutrition
- Asthma, Cystic Fibrosis and other Lung conditions
- Heart Disease
- Coeliac, Inflammatory Bowel Disease & other intestinal disorders
- Kidney Disease
- Liver Disease
- Rheumatoid arthritis
- Metabolic disorders
- Other Long-term Disorders

Mostly, the diseases will be obvious but sometimes poor growth is the presenting problem. Hence the doctor will order blood tests for these conditions when a short child is investigated (*see Table 1*).

Psychosocial Short Stature

Children in situations where home life is severely disrupted or unhappy, often experience emotional stress and poor growth. The growth failure is due to a combination of factors including, a decrease in the secretion of growth hormone, the body's response to growth hormone and poor nutrition.

If intervention by a social worker or psychologist fails, the only solution to this disorder may be to remove the child temporarily from the disrupted social situation and provide normal emotional, physical and nutritional support elsewhere. Growth in these children then recovers rapidly.

Tall Stature

Tall stature generally has less disadvantage than short stature. Only very tall or rapidly growing children require assessment. The most likely cause of tallness is genetic trait from one or both parents. The genetic tendency in height can be calculated by estimating the same sex mid parental height (*see Table 3*).

The assessment of tall stature follows much the same lines as for poor growth. After careful body measurements an estimation of final (adult) height is made by X-raying the hand and wrist for the level of skeletal maturation and using the height and a set of tables to predict the final height. When the predicated final height is much greater than the parent's height, consideration is given to further investigation and to interventions than may limit growth and reduce final height.

Historically, otherwise normal, but very tall boys and girls had their adult height reduced by advancing maturation (and adolescence) with the appropriate sex hormones in high dosage – testosterone in boys and oestrogen in girls. This therapy is undertaken very rarely nowadays. Side effects of treatment are common and long-term adverse outcomes have been reported.

Occasionally tall stature is due to inherited disorder such as Marfan Syndrome, genetic disorders such as Klinefelter Syndrome or Sotos Syndrome, early puberty (precocious puberty) or an endocrine disorder.

Genetic Disorders Causing Tall Stature

Marfan Syndrome

Marfan Syndrome is a rare inherited disorder that may affect many organ systems including bones, eyes, heart and blood vessels. Children with Marfan Syndrome have excessively long limbs with long thin fingers and very mobile joints. They are long babies at birth. They may be near-sighted (myopic) and at risk of more serious eye disorders. All children with Marfan Syndrome are tall and loose jointed and they may require limitation of their height to improve the mechanics of their loose joints. The diagnosis can be made by DNA (genetic) studies. Some of the most worrying problems occurring in Marfan Syndrome are abnormalities of the heart valves and dilation of the main arteries. All children with Marfan Syndrome need regular check-ups with specialists in various fields to ensure early detection and treatment of any problems.

Klinefelter Syndrome

This syndrome occurs in about 1 in 580 boys and promotes more rapid growth and tall stature particularly after 8 years of age. The problem is genetic and relates to the boy having 1 extra X chromosome, 47XXY.

Other problems can include some learning difficulties and abnormalities in physical development. All men with Klinefelter Syndrome have reduced fertility due to reduced sperm counts and adolescent boys have smaller testicles than normal.

Table 5 : SEX CHROMOSOMES IN HUMANS

Boys/men	46 XY
Girls/women	46 XX
Turner syndrome	45 X (or variants)
Klinefelter syndrome	47 XXY (or variants)
Triple X Syndrome	47 XXX

Many boys with Klinefelter Syndrome benefit from male (testosterone) hormone treatment in adolescence and / or later in life to promote male physical and behavioural characteristics. Testosterone use should be discussed with the specialist and is only used when needed.

Sotos Syndrome

This syndrome is an example of a number of rare conditions where rapid growth and tall stature are associated with an abnormality of the nervous system. Children with Sotos syndrome have delayed intellectual development associated with large brains and head size and characteristic facial features that a paediatrician can recognise. Fortunately, bone maturation advances faster than normal and although they become tall adults, these children do not remain as significantly tall as they appear in childhood years. No growth treatment is required.

Other Genetic Causes

There are a number of rarer genetic disorders which result in tall stature. These are either chromosomal disorders (e.g. 47 XYY Syndrome, 47 XXX Syndrome) or specific gene defects, which result in a characteristic appearance along with rapid growth and tall stature. These conditions can be recognised by a paediatric endocrinologist or a specialist in human genetics. Often there are specific tests to confirm the doctor’s suspicions of a specific diagnosis. Growth patterns in this group of disorders vary widely but, a specific diagnosis can be most useful in predicting the outcome for an individual child.

Premature Sexual Maturation

Premature sexual maturation is a term that describes a group of children who grow rapidly (out pace their peers), and cross centile lines on the growth chart in an increasing direction (*see Diagram 3*). The increased growth rate is accompanied by pubertal changes e.g. the appearance of breasts and genital growth. These changes are due to the sex hormones of puberty being produced abnormally early. Another term for this diagnosis is precocious puberty. There are many causes for this problem, including a genetic tendency to early adolescence. The doctor can advise on the treatments available to arrest rapid growth and sexual maturation if necessary.

Any child who is growing and maturating rapidly requires medical assessment as some of the causes have very serious implications.

Other Hormonal Causes

Growth Hormone Excess

Excessive growth hormone produced by the pituitary gland is usually due to a tumour and will cause rapid growth and advance bone maturation. This condition is rare in childhood. When it does occur it is often associated with headaches, problems with eyesight and other nervous system complaints. Urgent medical assessment by a specialist is needed.

> “Any child who is growing and maturing rapidly requires medical assessment as some of the causes have serious implications”

Throtoxicosis

The first sign of thyroid hormone excess may occasionally be rapid growth as thyroxine, the main hormone from the thyroid gland, promotes growth of long bones. An overactive thyroid causes other symptoms including a large thyroid (goitre), a rapid heart rate, fatigue and nervousness with behaviour problems including poor attention span. Medical or surgical treatment of the overactive thyroid condition corrects the growth problem.

Growth Hormone Treatment

Some children with poor growth benefit from the administration of growth hormone. The doctor's recommendation to begin a child on a course of growth hormone is based on many factors including a complete evaluation of the child's growth pattern, general health, medical and family history, the results of appropriate laboratory tests and the diagnosis. In addition, the child must fulfil conditions set by the Government so that the supply of the hormone can be provided through public health system. All modern growth hormone is made in a chemistry laboratory and is not a human product.

Availability of Growth Hormone

Growth hormone is available in either daily or weekly formulations. There are several brands of growth hormone available and although they vary in formulation, all brands of growth hormone have been shown to be effective in promoting growth in hormone deficient children.

Dosage and Administration

The dosage of growth hormone is calculated from the weight and height of the child (Body Surface Area) or in some cases on a child's weight. In both circumstances the dose will increase as the child grows. In certain circumstances the doctor may increase the dose if the child does not respond adequately.

"Please discuss the options available with the doctor"

Growth hormone is given by an injection just under the skin. To mimic the body's natural production, it is recommended that growth hormone be given before bedtime each night especially for daily growth hormone.

Frequency of Growth hormone

Depending on the type of growth hormone your child qualifies for will guide frequency.

All children who fulfill conditions set by the Government can access daily growth hormone. This treatment is administered 6 – 7 nights per week, depending on the dose required.

At present only children with growth hormone deficiency and those who qualify under the criteria of short and slow growth can access the long acting growth hormone. This treatment is administered weekly, in either one or two injections depending on the dose required.

Your child's endocrinologist will assist you in choosing an appropriate growth hormone formulation.

Storage of Growth Hormone

Incorrect storage can reduce the effectiveness of the growth hormone injections. As growth hormone is susceptible to temperature extremes, please store it according to the manufacturer's guidelines. If travelling with growth hormone, please seek the advice of your Health Care Professional on appropriate storage requirements.

Supply of Growth Hormone

Growth hormone is provided in 3 month supplies once the Government authority has been granted. Supplies are delivered to a patient's nominated community or hospital pharmacy. The height and weight of a child on growth hormone treatment will need to be measured on a 3 to 6 monthly basis and the doctor will need to provide details of the child's response to growth hormone every 6 months, to obtain further supplies.

Growth Hormone Injections

Growth hormone can be given via needle and syringe, injector pen, or electronic auto-injector. Please discuss all options available with your Health Care Professional to determine which devices are available in your country and the delivery option that is best suited to you.

Coping with Injection Problems

It is never easy explaining to children that injections are for their own good but there are ways of making the process easier. Try to develop a routine, giving the child a familiar toy to hold and using the same location such as a sofa or bed. Take time to create a relaxed atmosphere and explain the process to the child.

It is recommended that the child does not see the injection preparation process and therefore it is usually best for it to be done out of sight. The establishment of a quick, "no-fuss" procedure often ensures that children grow to accept their injections readily. For those who are anxious about giving/seeing the injection, options are available to help overcome this hurdle. The doctor or endocrine nurse can provide you with information about injection techniques and hospital growth clinics offer support programs and other advice.

When is Treatment with Growth Hormone Stopped?

In growth hormone sufficient short children, growth hormone therapy will stop once they reach skeletal maturity. This usually occurs at 13-14 years in girls and 16-17 years in boys, however, bone maturation can occur earlier or later than these ages. In some children, growth hormone treatment is stopped before skeletal maturity if there has been sufficient “catch-up” growth to bring the child into the normal range for their age, although care should be taken that they don’t lose these gains if they cease too early.

In growth hormone deficient children, treatment with growth hormone should be life-long even after reaching skeletal maturity. Currently in Australia, growth hormone has been approved as an indication for treatment in adults who meet eligibility criteria. This should be discussed with your endocrinologist.

Questions and Answers

About Growth Hormone Treatment

How does growth hormone work?

Growth hormone increases the size, number and protein content of cells in the growing body. The amount of muscle, bone and connective tissues increases whilst the skeleton lengthens and widens. At the same time body fat is reduced. The child starting on growth hormone loses fat without losing weight and gains muscle strength and bone structure. Some children find their appetite increases and increased food intake adds to the effect of the growth hormone.

Are there any side-effects to growth hormone treatment?

Like all medicines, growth hormone therapy may occasionally cause unwanted side effects, such as skin reaction at the injection site and less often, headaches, swelling of the arms or legs and limping. Children with bone disorders (e.g. hip problems, scoliosis) need to be closely monitored, because rapid growth can aggravate these problems. To avoid this the doctor may start the child on a small dose of the hormone and gradually increase it until the full dosage is reached. Other rarer side-effects can occur, though these usually only happen in children who have a separate pre-existing condition and therefore an increased risk of developing these rare effects. If you are concerned that your child may be experiencing side effects as a result of growth hormone therapy, you should contact your doctor or endocrine nurse as soon as possible.

Why would the doctor recommend growth hormone treatment?

To be considered for growth hormone therapy, a child is usually at or less than the first centile for height on an endorsed growth chart and growing extremely slowly. For children who have developed growth hormone deficiency after brain tumour treatment they only have to demonstrate growth failure, and may not be very short.

Treatment is started based on many factors, including a complete evaluation of his/her growth pattern, general health, medical and family history, bone age x-ray, test results and diagnosis. There are usually three reasons for starting therapy:

1. To achieve "catch-up" growth to bring the child in line with peers
2. Improve self-esteem and reduce social discrimination
3. Long-term to significantly improve adult height

Aims 1 and 2 are always part of the recommendation.

Should children give their own injections?

Children should feel involved in the administration of their injections, and the initial device choice if possible. If they can give their own growth hormone injection it is easier for them to attend school camps and sleepovers etc. Around the age of 9 years, some children may decide to give their own injections. They should, however, always be supervised by an adult.

Where should injections be given?

Growth hormone injections are given under the skin in the legs, arms abdomen or buttocks. It is important to use different injection sites every day.

What if an injection is missed?

There is no adverse reaction to missed injections, however, for optimal growth outcomes to be achieved, it is important that injections are given regularly, according to the schedule prescribed. Missing injections can lead to less efficient growth. Also, if too many injections are missed, ongoing funding for growth hormone treatment may be affected. Therefore, please talk to your Health Care Professional about what to do in the case of missed injections.

Are there any drugs or treatment that should not be taken during treatment with growth hormone?

Tell the doctor if the child is taking other medication before starting to use growth hormone. Some medications may interfere with the effect of growth hormone, however there are no known drugs which are incompatible with growth hormone as it is made naturally by the body.

Glossary

Anabolic Steroids
Synthetic male sex hormones that promote tissue and bone growth.

Biosynthetic Hormone
Manufactured hormones that are identical to or perform the same function as those made naturally by our bodies.

Cardiologist
A doctor who specialises in disorders of the heart and circulation.

Cartilage
Soft gristle material at the end of long bones, some of which hardens into bones when growth is complete.

Chromosome
A thread like structure that carries genetic information in the form of genes composed of DNA. Normally, each human cell contains 23 pairs of chromosomes, one pair of these are the sex chromosomes. Genes and chromosomes are like blueprints for the body's development, and so play a large part in determining a person's characteristics.

Congenital
A feature or condition that is present from birth, but not necessarily hereditary.

Corticosteroids
Steroid hormones produced by either the adrenal gland or synthetic process. Examples include cortisone, hydrocortisone and prednisone.

Cyanotic Heart Disease

Heart conditions in which arterial and venous blood mix. The overall oxygen content of the blood is lower resulting in less oxygen delivery to the body.

Cystic Fibrosis

A hereditary disease that affects secretory glands, (i.e. sweat glands, mucus-secreting glands and pancreas). Children with cystic fibrosis experience frequent chest infections, digestive problems as well as poor growth.

DNA

Stands for Deoxyribonucleic Acid and is the chemical that forms the genetic code.

Endocrine Gland

A gland that makes hormones and release them into the blood. The pituitary, thyroid, adrenal, testes (testicles) and ovaries are all endocrine glands. All of the glands together make up what is termed the endocrine system.

Endocrinologist

A doctor who specialises in the disorders of the endocrine glands.

Endoscope

An instrument used to visualise the inside of the body. Most endoscopes consist of a narrow, mobile tube with a light and a camera to transmit the images to the eye or a screen.

Foetus
The developing baby in the womb from the ninth week of pregnancy until the moment of birth.

Gastroenterologist
A doctor who specialises in the disorders of the digestive tract.

Genetic potential height
The adult height calculated from the heights of the parents.

Hormones
Blood chemicals that perform many roles, including stimulating growth and sexual development and helping to regulate the body's metabolism. Normally the body carefully controls the release of hormones as too much or too little may disrupt the body's delicate balance. They are produced by endocrine glands and carry messages from one cell to another via the bloodstream.

Hypothalamus
Part of the base of the brain that controls the release of hormones from the pituitary gland.

Idiopathic
The term used to describe the situation when no reason can be found to explain the cause of a disease or disorder.

Intrauterine
Within the uterus (womb).

Karyotype

The chromosome set of an individual. For example the karyotype of a girl with Turner Syndrome is usually 45X.

Oestrogen

A group of female hormones that are produced by the ovaries from the onset of puberty and continuing until menopause, which controls female sexual development.

Paediatric Endocrinologist

A doctor who specialises in the disorders of endocrine glands in children.

Pituitary gland

A pea-sized gland at the base of the brain, which releases a number of important hormones related to normal growth, development and fertility, including growth hormone.

Placenta

The organ which connects the foetus to the wall of the uterus. The placenta provides the foetus with nourishment and eliminates wastes.

Puberty

Essentially the period in a young person’s life, both male and female, where they become physically capable of reproduction.

Skeletal maturity

This is when there is no further growth in the bones, because the growth plates have fused.

Somatomedins
These are hormones made by the liver that deliver the growth message to the bones and other tissues. Somatomedins are stimulated by growth hormone.

Subcutaneous Injections
An injection given beneath the skin.

Syndrome
A syndrome is a collection of characteristics that occur together and characterise a particular condition.

Testosterone
Most potent male sex hormone, which is produced in the testes (testicles) and controls male sexual development.

Thyroid Gland
A butterfly-shaped gland in the front of the neck below the larynx, which makes the hormone thyroxine.

Turner Syndrome
A congenital chromosomal disorder occurring in females caused by the absence of one X chromosome. Short stature is a common symptom in girls with Turner Syndrome.

X Chromosone
The female sex chromosome.

Y Chromosone
The male sex chromosome.

Support Organisations and Further Reading

Australia and New Zealand Society for Paediatric Endocrinology and Diabetes (ANZSPED)
www.anzsped.org

Australian Pituitary Foundation
www.pituitary.asn.au

Coeliac Society of Australia
www.coeliac.org.au

Down Syndrome Australia
www.downsyndrome.org.au

Down Syndrome Association NSW
www.downsyndromensw.org.au

Down Syndrome Association QLD
www.downsyndrome.org.au/qld

Down Syndrome Association Victoria
www.downsyndrome.org.au/vic

Down Syndrome Association South Australia
www.downsyndrome.org.au/sa

Down Syndrome Association Western Australia
www.downsyndrome.org.au/wa

Genetic Alliance Australia
www.geneticalliance.org.au

Genetic Support Network Victoria
www.gsnv.org.au

The Endocrine Society
www.endocrine.org/

Hormones Australia
www.hormones-australia.org.au

The Magic Foundation
www.magicfoundation.org

The Marfan Foundation
www.marfan.org

Turners Association
www.turnersyndrome.org.au

UK Society for Endocrinology
www.endocrinology.org

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Date of preparation: June 2024 | AU-NONE-00038

Hormones and Me

Growth Problems in Children

This booklet is valuable reading for children who have hormone problems affecting their growth.

It is also recommended reading for their family and friends.