Meet the Expert
HANDOUTS

These sessions are interactive. Seats are limited and will therefore be allocated on a "first-come, first-served" basis.

Statements on any potential conflict of interest will be shown by the speaker at the beginning of their session.

Opinions and recommendations made by the presenters are not those of ESPE.
Meet the Expert Session
1:1 – 1:2

Management of adrenal tumours

Constantine Stratakis (Bethesda, USA)

Thursday 1 October 16:00 – 17:00 – Hall 6
Saturday 3 October 08:00 – 09:00 – Hall 6
Meet the Expert Session
2:1 – 2:2

Translation of diabetes technologies
to clinical practice

Olga Kordonouri (Hannover, Germany)

Thursday 1 October 16:00 – 17:00 – Hall 5
Saturday 3 October 08:00 – 09:00 – Hall 5
Translation of diabetes technology to clinical practice
Meet the Expert Session
Olga Kordonouri, Hannover
Email to kordonouri@kika.de

Modern diabetes technology
systems of continuous glucose monitoring (CGM)

CGMS Gold or iPro2
- for physician’s orientation
- retrospective data analysis
- single diagnostic application

FreeStyle Libre
- for patient use
- real time values and trends
- replaces blood glucose measurement
- no alerts
- continuous use (lasts 14 days)

Real time sensors
- for patient use
- real time values and trends
- with alerts for high/low values and rapid glucose changes
- continuous use (5-7 days)
- therapeutic and educational tool

Current CGM systems with alerts

<table>
<thead>
<tr>
<th>System</th>
<th>Sensor site</th>
<th>Sensor length</th>
<th>Insertion angle</th>
<th>Max. duration</th>
<th>Time between placement and display</th>
<th>Calibration</th>
<th>New values</th>
<th>Display Options</th>
<th>Data Download</th>
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</thead>
<tbody>
<tr>
<td>CGMS Gold</td>
<td>23 Gauge</td>
<td>8 mm</td>
<td>90 degrees</td>
<td>14 days</td>
<td>2 hours</td>
<td>every 12 h</td>
<td>every 5 minutes</td>
<td>every 30 minutes</td>
<td>possible</td>
</tr>
<tr>
<td>iPro2</td>
<td>23 Gauge</td>
<td>6 mm</td>
<td>90 degrees</td>
<td>14 days</td>
<td>2 hours</td>
<td>every 12 h</td>
<td>every 5 minutes</td>
<td>every 30 minutes</td>
<td>possible</td>
</tr>
<tr>
<td>FreeStyle Libre</td>
<td>21 Gauge</td>
<td>8 mm</td>
<td>90 degrees</td>
<td>14 days</td>
<td>2 hours</td>
<td>every 12 h</td>
<td>every 5 minutes</td>
<td>every 30 minutes</td>
<td>possible</td>
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<tr>
<td>Navigator 2</td>
<td>21 Gauge</td>
<td>8 mm</td>
<td>90 degrees</td>
<td>14 days</td>
<td>2 hours</td>
<td>every 12 h</td>
<td>every 5 minutes</td>
<td>every 30 minutes</td>
<td>possible</td>
</tr>
</tbody>
</table>
Type 1 Diabetes (T1D) in toddlers: a daily challenge

- Rosa, 3 years old, T1D since 9 months of life
- Treatment with CSII (Paradigm VEO, Insulin Aspart) and CGM
- HbA1c 7.2 % (55.2 mmol/mol)
- Weight: 9.2 kg (37th-10th centile), Height: 78 cm (3rd centile)
  BMI 15.1 kg/m²

- No episode of severe hypoglycemia
- No episode of DKA
- No other chronic disease (i.e. celiac disease)
Key to success: Distinguish basal and prandial insulin need

Insulin is needed to cover:
- Endogenous glucose
- Exogenous glucose

Daily insulin requirements

<table>
<thead>
<tr>
<th>Age</th>
<th>Insulin dose (U/kg BW/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>0.8 – 1.0</td>
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<tr>
<td>Adolescents</td>
<td>0.8 – 1.2</td>
</tr>
<tr>
<td>Adults</td>
<td>0.6 – 0.7</td>
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<tr>
<td>Basal insulin requirement</td>
<td>0.3 – 0.4</td>
</tr>
</tbody>
</table>

The impact of diabetes technology

Positive Effect of CGM on HbA1c

J. Pickup et al., BMJ 2011
PILGRIM
Predictive Low Glucose Management in Realtime Sensing Insulin Pump Therapy
Cycles of 30 min Exercise

Admission to the research center

Overtight fasting
Stable 80-90-100 mg/dl

Pillbox/CT
Ext. Insulin
PILGRIM

Pump suspended when predictive threshold < 80
mg/dl is reached

CSC basal rate resumed

16:00 23:00 7:00 maximum 4 hours

Day Time Exercise

Proof of concept:
Significant prevention of hypoglycemia during exercise

Danne T et al. Diab Technol Ther 2014

Pump generations:
Steps toward to artificial pancreas
T1D in toddlers – how can technology help?

**Summary and recommendations**

* Toddlers daily life is characterized by a high level of spontaneity, long sleep, unpredictable eating habits, recurrent infections and high insulin sensitivity
* Mothers and other care giving have frequently pronounced fear of hypoglycemia
* Flexible insulin regimes, and particularly the use of modern insulin pumps (CSII) provide an individual tailored insulin treatment
* Download and evaluation of CSII data help the multidisciplinary diabetes team to understand diabetes/insulin management at home
  ✓ check for total daily dose, amount of basal insulin, frequency and kind of boluses, intervals of catheters changing
  ✓ compare frequency of glucose measurements and bolus shots
  ✓ in case of sensor-augmented CSII, check for duration of pump interruption (summary overview) and analyze glycemic daily profiles, respectively
* Clinical studies and routine experience demonstrate that continuous use of CGM can help even young children to achieve an optimal glycemic control without increase of hypoglycemia.

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**T1D and Sport**

- **Anna**, 19 y old, T1D since 14 y of life
  - Treatment with CSII (Paradigm VEO, Insulin Aspart)
  - HbA1c: 6.8% (50.8 mmol/mol)
  - running, cycling, nertball, hiking

- **Markus**, 17 y old, T1D since 13 y of life
  - Treatment with insulin Glargine and insulin Lispro
  - HbA1c: 6.9% (51.9 mmol/mol)
  - soccer (4,5-6 h/week), physical training (1h/week)

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**CGM and Sport**

**Blood glucose measurement**
- "sharp" as a picture
- "snapshot" of blood glucose level
- precise single value

**Continuous glucose monitoring**
- "dynamic" as a movie
- chronological sequence of glucose values
- less precise single values
- Diabetes management based on the trends
T1D & Sport – Summary and recommendations

- Take insulin regimen intact. Multiple daily injections or a pump may be easier to combine with active exercise.
- Discuss the percentage reductions in insulin before exercise:
  - When exercise is performed at a level of normal daily activity, a 15% reduction in insulin doses should be used.
  - The insulin needs to be decreased in line with the time and instrumental level of exercise with a 30% reduction for 1 hour before starting the exercise and a reduced dose if exercise is delayed.
  - Depending on the level of activity the decrease will be slightly increased to exercise intensity.
- Discuss type and amount of carbohydrates (CHO) required for specific activities.

K. Robertson et al., Ped Diab 2014

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**Diabetes Management @ the TIDYC**

<table>
<thead>
<tr>
<th>Ita</th>
<th>Mark</th>
</tr>
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<tbody>
<tr>
<td>Mean glucose (mg/dL)</td>
<td>140.0 ± 48.3</td>
</tr>
<tr>
<td>Glucose in target range</td>
<td>30.9%</td>
</tr>
<tr>
<td>Glucose below target</td>
<td>23.0%</td>
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<tr>
<td>Glucose above target</td>
<td>25.9%</td>
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<tr>
<td>Total daily insulin dose</td>
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<td>Total basal insulin</td>
<td>9.0</td>
</tr>
<tr>
<td>Total basal insulin</td>
<td>9.0</td>
</tr>
</tbody>
</table>

K. Robertson et al., Ped Diab 2014

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References and Literature

Meet the Expert Session
3:1 – 3:2

Challenges in the management of short stature
Jesús Argente (Madrid, Spain)

Thursday 1 October 16:00 – 17:00 – Hall 3
Saturday 3 October 08:00 – 09:00 – Hall 3
MINI-REVIEW

54th ESPE Annual Meeting, Barcelona, Spain, October 1-3, 2015

MEET THE EXPERT SESSION (MTE)

Title: Challenges in the management of short stature

Short title: Short stature

Key words: Short child, short stature, short for gestational age, SGA, growth hormone deficiency

AUTHOR: Jesús Argente

INSTITUTIONS:


Abstract: 199 words

Total words: 3228

Tables: 2

Figures: 1

ESPE Member

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ABSTRACT

Human growth, from the fetus to adolescent, is dynamic and the best marker of health. Growth is a complex process influenced by genetic, hormonal, nutritional and environmental factors, both pre- and postnatally. To date no international agreement regarding normal height has been established. Auxological parameters are fundamental to investigate potential short stature, either with a know diagnosis, e.g., disproportionate or proportionate, prenatal and/or postnatal onset, or an unknown diagnosis, i.e., idiopathic short stature. The incidence/prevalence of short stature is difficult to establish. The measurement of choice in children aged less than 2 years is length, while in those over 2 years of age it is height.

A number of monogenic diseases that lead to proportionate short stature due to either isolated GH deficiency, multiple pituitary hormone deficiency, GH insensitivity, primary ALS deficiency, primary IGF-I deficiency, IGF-I resistance, primary IGF-II deficiency or primary protease deficiency have been discovered in the last thirty years. In addition, “The Nosology and Classification of Genetic Skeletal Disorders” revised in 2010 includes 456 conditions, 316 of which are associated with mutations in one or more of 226 different genes. A practical algorithm for evaluation of short stature is discussed, as well as the therapeutical options.

INTRODUCTION

Human growth is regulated by genetic, hormonal, nutritional and environmental factors that interact to culminate in a complex process of constant replication of cells in all tissues (1). Human growth is characterized by several phenomena: dramatic fetal growth (when growth is most rapid), deceleration of growth immediately after birth, prolonged growth during childhood that is followed by prepubertal deceleration, and a pubertal growth spurt.

Short stature (SS) in childhood is a very frequent reason for referral to pediatric endocrinologists (2,3). Normal height is determined according to the age, sex and ethnic group, as well as the family context. In clinical practice, we compare the projected adult height of a subject with their “target height” (TH) or “genetic height”. However, growth is a dynamic process such that normal height at one specific moment does not exclude the possibility of SS occurring later in development. Hence, growth velocity (GV: Δ height/year) is employed. These methodological difficulties are responsible for our inability to establish a cut-off that clearly discriminates between “normal” or “pathological” height and contribute to the lack of an international consensus clearly establishing the concept of SS/under growth. The criteria most commonly used in clinical practice are:
• Height below -2 SDS (percentil 2.3) for age, sex and ethnic group (≈ percentile 3/ -1.88 SDS).

• Height that although is between ± 2 SDS for the general population, it is more than 2 SDS below the growth curve corresponding to the patient’s TH.

• Projected adult height (prediction of adult height) more than 2 SDS below the TH.

• Persistent low GV.

There is also no international consensus regarding the definition of diminished GV, although a GV below -1 SDS (≈ percentile 25) for age and sex maintained for more than 2-3 years is considered to be “potentially” pathologic.

**Do we know the incidence/prevalence of SS?**

It is difficult to establish the incidence or prevalence of subjects with SS at one specific moment. The number of children with SS is possibly around 3-5%. The prevalence of GH deficiency is around 1 in 4000.

**How should growth be measured?**

In the newborn length, weight and head circumference according to gestational age are the most important parameters. The length of newborns and infants is measured in an infantometer. A child’s height is measured standing erect against a stadiometer.

In children older than 2 years, height, weight and head circumference are used. In addition, waist circumference and skin fold measurements can be employed. At each time-point length and height should be measured twice, with the difference of the two measurements being within 4 mm. To obtain an accurate weight the scale must be correctly calibrated.

**Do we have standarized growth charts?**

The techniques to evaluate growth are well standarized (1). The WHO international charts (2006) represent standard growth for healthy children and are currently recommended for children <2 years. For children older that 2 years local growth charts should be employed, in particular those including longitudinal studies where SDS GV can be analyzed. Local charts should also be used for weight, particularly in occidental communities where overweight and obesity, especially in adolescents, are more common. Transversal studies are of interest to rapidly establish the median nd extreme weights per chronological age.
ETIOLOGY & CLASSIFICATION

SS can be classified into two main groups: known and unknown etiology. Amongst known etiologies proportionate and disproportionate SS can be included, both of which can be either congenital or acquired. Among children with proportionate SS, we should distinguish between prenatal and postnatal origin. In children classified as having SS of unknown etiology with the diagnosis of idiopathic short stature (ISS), it is common that “normal variants of SS” [familial short stature (FSS)] and constitutional delay of growth and puberty (CDGP) are also included (Table I).

I. Osteochondrodysplasias

The *Nosology and Classification of Genetic Skeletal Disorders*, revised in 2010 (4), provides an overview of 456 conditions included in 40 groups defined by clinical, radiographic, biochemical and molecular criteria. Among these conditions, 316 are associated with mutations in one or more of 226 different genes. The most common conditions seen by the pediatric endocrinologists are included here as it is beyond the scope of this review to go into further detail.

**Achondroplasia**

Achondroplasia is the most common non-lethal skeletal dysplasia (ACH; MIM:100800), with a prevalence between 1/16,000 and 1/26,000 live births (5). It is due to mutations in the fibroblast growth factor receptor 3 (*FGFR3*, OMIM# 134934) gene (approximately 98% show a G to A point mutation at nucleotide 1138) and inheritance is autosomal dominant with essentially complete penetrance. Its main characteristics include a large head with prominent forehead, small midface or midface hypoplasia, flattened nasal bridge, nonproportional dwarfism (adult ≈ 131 cm), spinal kyphosis or lordosis, shortening of the proximal limbs (rhizomelic), short fingers and toes and varus or valgus deformities. The “trident hand” (the 3rd metacarpal is short, the 4th deviated to the ulnar side and the thumb is radially displaced) is characteristic.

**Hypochondroplasia**

Hypochondroplasia (HCH, MIM: 146000) is a milder form of achondroplasia due to mutations in the *FGFR3* gene (4). Patients exhibit relatively short extremities with moderate narrowing of the interpedicular distances, increased dorsal concavity of the vertebral bodies, short and broad femoral necks, disproportionate long fibula, short plump tibia and moderately short plump humerus.

**Multiple Epiphyseal Dysplasias**

This is an autosomal dominant osteochondrodysplasia. It is a clinically and genetically heterogeneous disorder characterized by mild SS and early-onset osteoarthritis (6). The phenotypic
spectrum includes edgy (not rounded) carpal bones, femoral capital epiphyses and greater trochanter are smaller than usual but regular in shape, the acetabular roof shows the beginning of degenerative changes, irregularities of the epiphyseal contours in the knee, wedging of the metaphyses and small patella.

At least five genes have been implicated in the different types of multiple epiphyseal dysplasias: COMP, COL9A1, COL9A2, COL9A3, MATN3.

**Léri-Weill Dyschondrosteosis (LWD)**

LWD (LWD, MIM 127 300) is characterized by mesomelic limb shortening and the characteristic Madelung deformity. Most LWD cases are caused by heterozygous mutations in SHOX or its regulatory regions located in PAR1 (7-9). Heterozygous SHOX mutations are also observed in a small proportion (2-5%) of patients with ISS (ISS, MIM 300 582).

**Langer Mesomelic Dysplasia (LMD)**

LMD (MIM 249700) is associated with defects in both copies of SHOX, and characterized by severe disproportionate short stature and mesomelic and rhizomelic limb shortening (10).

**Acromesomelic Dysplasia Type Maroteaux (AMDM)**

AMDM (MIM 602875) is caused by biallelic loss of function mutations in the natriuretic peptide receptor B/guanylate cyclase B gene (NPR2), while heterozygous mutations in NPR2 cause familial SS (11,12). Patients with AMDM exhibit severe disproportionate SS, shortening of the extremities, bowing of the forearm and shortening of metacarpals and phalanges.

**II. PROPORTIONATE SHORT STATURE**

**Prenatal origin**

This includes patients with SS due to fetal (chromosomopathies, different syndromes and what is now called “primordial dwarfism”), uterine or placental features or maternal pathology (malnutrition, drugs, alcohol, tobacco, cardiac pathology or congenital infection). Silver-Russell, Seckel, Cornelia de Lange, Noonan and Prader-Willi are amongst the most common syndromes.

A newborn is considered small for gestational age (SGA) when their birth weight and/or length are at least 2 SDS below the mean for gestational age (≤ -2 SDS) (13). In developed countries, 4-7 % of newborns are SGA. When the newborn shows a combined diminution of length and weight at birth (proportionate SGA) the risk of SS is higher than if only the weight is affected (disproportionate SGA).
Characteristically, 80-90% of SGA subjects experience partial or complete catch-up growth during the first or second year of extrauterine life, reaching a height into the normal range (± 2 SDS). In contrast, the other 10-20% remain short after 2 years of life, 50% of which will have a low adult height.

One third of SGA newborns are due to fetal factors (chromosomopathies, congenital abnormalities and different syndromes), with the rest being due to maternal (malnutrition, infections, toxins) and placental-uterine (uterine malformations, single umbilical artery) factors. In 40% of cases no abnormalities are found.

**Postnatal origin**

**A. GH deficiency**

Of the causes of proportionate SS due to endocrinopathies (around 5%), here we concentrate on the genetic alterations of the GH-IGF axis. GH deficiency (GHD) represents 1-2% of SS (prevalence 1 in 4000). GHD can be isolated or combined with other pituitary deficiencies (MPHD) and can be congenital or acquired (tumors, traumas, histiocytosis, infections, radiotherapy). In most cases GHD is idiopathic (the organic cause is identified in only 20%). Among the idiopathic cases, abnormalities in the MRI (pituitary hypoplasia, lack of pituitary stalk and ectopic posterior pituitary) are frequent.

The most common characteristic of GHD is the failure to grow, including a dramatic reduction in GV and delayed BA. Spontaneous GH secretion and/or the GH response to different stimuli are reduced, as well as serum IGF-I and IGFBP-3 levels. The congenital forms are severe and growth failure is precocious (14-17). Growth failure can be present in the first months of life with a characteristic phenotype: doll face, high pitch voice, increased periabdominal fat, acromicria, and decreased muscle mass. Congenital GHD can be associated with perinatal complications (hypoglycemia, small penis, neonatal ictericia). When GHD is acquired, the SS manifests later and can be the only clinical manifestation. The genes implicated are GH1 and GHRHR.

Mutations in POU1F1 (18), PROP1 (19), LHX3 (20) and LHX4 (21) are associated with MPHD. Other genes involved in MPHD include HESX1 (22), SOX2 (23), SOX3 (24), OXT2 (25), GLI2 (26) and RNPC3 (27).

**B. GH insensitivity**

GH insensitivity (GHI) is caused by mutations in the GH receptor (GHR), with Laron syndrome being described in 1966 (28). Numerous mutations have been reported in the external, internal and transmembrane domain (29) of the GHR, with endogamic populations existing (30). The first GHR
mutations producing “partial GH resistance” were reported in 1995 (31). Mutations in STAT5b have also been described (32).

C. **Primary ALS deficiency**

The IGF acid-labile subunit (IGFALS) is a glycoprotein found in the circulation and produced in the liver under GH stimulation. This subunit stabilizes the IGF–IGF-binding protein (BP) 3 complex. Mutations in IGFALS produce SS (33-35).

D. **Primary IGF-I deficiency**

IGF-I mediates most of the growth-promoting effects of GH after birth. It is important to note that while GH is not implicated in prenatal growth, IGF-I is. Woods et al described the first patient with a homozygous partial deletion of the *IGF-I* gene that presented with severe prenatal and postnatal growth failure, sensorineural deafness and mental retardation, (36).

E. **IGF-I resistance**

Mutations in the *IGF-IR* gene underlie some cases of prenatal and postnatal growth failure (37). These patients are phenotypically distinct from the patients with the *IGF-I* gene mutation described by Woods et al. *IGF-IR* gene variants, including heterozygous *IGF-IR* mutations or haploinsufficiency of this gene, should be investigated in subjects with familial SS (38).

F. **Primary IGF2 deficiency**

The first *IGF2* variant (c.191C→A, p.Ser64Ter) was recently described in four family members with growth restriction (39). Their severe growth restriction suggests that IGF-II affects postnatal growth, in addition to prenatal growth. Moreover, the dysmorphic features of the affected subjects are consistent with deficient IGF-II levels as a cause of Silver-Russell syndrome (39).

G. **Primary protease deficiency**

We recently reported the first patients with a mutation in *PAPP-A2*, producing a new syndrome with SS (40).

Hence, we propose a new classification for the molecular basis of proportionate SS and look forward to a future international consensus (Table II).

H. **Other endocrinopathies**

**Hypothyroidism** represents <1% of patients with SS. Due to the universal application of neonatal screening, this figure has declined in recent years.
Patients with chronic hypercortisolism exhibit SS together with generalized obesity. Hypercortisolism is due to ACTH hypersecretion (Cushing’s disease), adrenal production of cortisol (Cushing’s syndrome) or to long-term exogenous administration of glucocorticoids.

Excess sex steroids (precocious puberty either gonadotropin-dependent or independent) produces abnormal acceleration of GV and BA with transitory overgrowth, but short adult height.

Pseudohypoparathyroidisms represent a heterogenous group of diseases due to PTH resistance. These patients show hypocalcemia, hyperphosphatemia and high PTH levels, with no increase in 1-25 (OH)₂ or hyperphosphaturia. In addition, some patients exhibit SS, obesity, a round face, moderate mental retardation and bone abnormalities (Albright hereditary osteodystrophy).

III. IDIOPATHIC SHORT STATURE (ISS)

An international consensus to define ISS established (41) that “ISS is defined auxologically by a height below 2 SD score (SDS) with no findings of disease as evident by a complete evaluation by a pediatric endocrinologist including stimulated GH levels. Magnetic resonance imaging is not necessary in patients with ISS. ISS may be a risk factor for psychosocial problems, but true psychopathology is rare”. In the United States and seven other countries, the regulatory authorities approved GH treatment (at doses up to 53 g/kg/day) for children shorter than 2.25 SDS, whereas in other countries, lower cutoffs are proposed. “Specifically, children with ISS have normal birth weight and are GH sufficient. ISS describes a heterogeneous group of children consisting of many presently unidentified causes of SS. It is estimated that approximately 60–80% of all short children at or below 2 SDS fit the definition of ISS”. This definition of ISS includes short children labeled with constitutional delay of growth and puberty (CDGP) and familial short stature (FSS). Hence, “children with dysmorphic phenotypes or SGA should be excluded from the ISS diagnostic category as they are children with clearly identified causes of SS”. Wit et al. also established a definition for ISS (42) and have discussed the management of ISS (43).

It is not clear whether FSS and CDGP will be classified as ISS in the future. Time will tell whether we can be more precise in the diagnosis of FSS (healthy short subjects, with normal maturation and relatives with SS), CDGP (healthy subjects with slow maturation, -2 to 3 years of BA, that exhibit SS when they are children and start puberty with a delay, obtaining adult height at an age greater than the population mean). In both situations, the adult height is according to the familial context.

The concept of ISS is controversial, artificial, arbitrary and heterogenous, including normal and pathological patients, having one thing in common: our ignorance to obtain an etiopathogenic diagnosis. Around 80% of the children that visit a pediatric endocrinologist could be included in the
concept of ISS. Most of them (80-85%) will be what we have called normal variants. Research and new methodologies will allow new diagnosis of patients labeled as ISS, creating new classifications of groups of known pathology.

IV. EVALUATION FOR DIAGNOSIS OF SHORT STATURE

The initial evaluation of every child with SS should include patient history, family history, a complete physical exam, bone maturation (bone age), pedigree and, if possible, the analysis of his/her pattern of growth with the data from the parents. With these data, we should be able to conclude whether the patient has SS, if it is proportionate or disproportionate and if it is of prenatal and/or postnatal origin. Subsequent complementary studies should be done to try to make a specific diagnosis and to determine whether a therapeutical procedure could be used.

A practical algorithm of the evaluation of SS is included in Figure 1.

- If SS is disproportionate, a skeletal survey should be done. In addition, molecular studies for the most common skeletal dysplasias are indicated (FGFR3, SHOX, NPR2, COMP, COL9A1, COL9A2, COL9A3, MATN3).

- If SS is proportionate and of prenatal origin, chromosomopathies and syndromes should be analyzed. A karyotype is indicated to discard chromosomopathies. If there is suspicion of a specific syndrome with a known molecular defect, molecular studies should be done. If there is no orientation to a specific diagnosis, genome-wide association studies or exome studies might be indicated.

- If SS is proportionate, of postnatal origin and not very severe (between -2 and -3 SDS) in most cases the diagnosis will be a normal variant of SS or ISS. If SS is more severe (> -3 SDS) it is necessary to explore other diagnoses including GHD, celiac disease, Crohn’s disease, hypothyroidism, among others.

- There are significant controversies in the diagnosis and management of GHD (44). Hence, an early reassessment of the diagnosis in patients that respond poorly to treatment is recommended (45).

- If we do not have a specific diagnosis and the SS is severe or has a familial component, the possibility of performing an exome study should be considered (46).

V. THERAPEUTICAL APPROACH TO SHORT STATURE
In many cases, SS does not require treatment and a conversation with the parents and child would be the most important medical action. To wait and see the patient every six months is the correct action.

If there is a specific diagnosis of organic pathology, we should treat it (celiac disease, Crohn’s disease, cardiopathy, cystic fibrosis, hypothyroidism, hypercortisolism).

The therapies available to improve growth are limited: hrGH, hrIGF-I, GnRH analogs, aromatase inhibitors (anastrozole and letrozole) and bone enlargement surgery.

hrGH therapy is approved by EMA in patients with GHD, SGA, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency and abnormalities in the SHOX gene. The FDA has approved all of the above plus Noonan syndrome and ISS. Time will tell whether all of these indications continue accepted:

→SGA patients show a very heterogenous response and we need to know why. →Although hypotonia improves slightly in some patients with Prader-Willi, most of them dramatically increased heighy and weight. Is this really what we want? →The response in patients with chronic renal insufficiency is quite modest, with some not responding at all.

→GH is not indicated in most patients with SHOX abnormalities, as their height is greater than -2.5 SDS. Not all patients with SHOX alterations and height less than -2.5 SDS respond well and some develop pain in the wrists. Is a dysplastic bone prepared to recieve hrGH?

→Pediatric endocrinologists are concerned about the high serum IGF-I levels in patients with Turner syndrome under GH therapy. Hence, potential side effects should be analyzed in the future.

→Should we treat Noonan patients with mutations in the proto-oncogene PTPN11? Again, we will only know in the future.

→Should we treat patients with ISS? (47) The door would be open to almost any child with SS, but is this correct?

Long-term hrGH therapy appears to be effective and safe in patients with GHD. The future will delineate the indications of its use, including new diseases and other skeletal dysplasias.

hrIGF-I therapy has been approved for patients with severe primary IGF-I deficiency (IGFD). The number of patients is low. Long-term therapy with IGF-I improves AH of patients with severe IGFD, although most patients do not experience catch-up growth sufficient to obtain a height in the
normal range (48). Hence, long-term IGF-I therapy appears to be effective and relatively safe as a replacement therapy in children with SS due to severe IGFD.

The same conclusions are presented in a recent manuscript reporting the European experience (49).

Backeljauw et al (50) described the first study to test the efficacy and safety of coadministration of rhGH and rhIGF-1 (45/150 µg/kg) in children with SS. Linear growth was significantly accelerated compared to rhGH alone, with a safety profile similar to the individual monotherapies. However, the results support the use of combination of GH and IGF-I in selective cases and not universally (51).

- GnRH analogs together with hrGH could be effective in increasing adult height in GHD children (52). It is still uncertain if aromatase inhibitors could effectively improve adult height in early pubertal boys with GHD or ISS (52).

**Figure and Table legends**


Table 2. Known molecular basis of proportionate short stature.

Figure 1. Algorithm for diagnosis of short stature.
REFERENCES


I. SHORT STATURE OF KNOWN ETIOLOGY

A. DISPROPORTIONATE

a) CONGENITAL: Skeletal displasias:
   - Groups 1-8: Based on a common underlying gene or pathway
   - Groups 9-17: Based on radiographic changes with clinical features:
     - Acromesomelic displasia Type Maroteaux (NPR2 -9p13-12)
     - Léri-Weill Dyschondrosteosis (SHOX –Xpter-p22.32)
     - Langer Dyschondrosteosis (SHOX –Xpter-p22.32)
   - Groups 18-20: Macroscopic criteria with clinical features
   - Groups 21-25 & 28: Based on mineralization abnormalities
   - Group 26: Hypophosphatemic disorders
   - Group 27: Lysosomal disorders
   - Group 29: Developmental skeletal disorders (exostoses, enchondromas)
   - Group 30: Overgrowth disorders (Sotos, Marshall, Marfan, Beals)
   - Group 31: Genetic inflammatory/rheumatoid-like osteoarthropathies
   - Groups 32-40: Dysostoses (affecting individual bones or groups of bones)

b) ACQUIRED: Secondary to malformations, radiotherapy, tumors and other diseases

B. PROPORTIONATE OF PRENATAL ORIGIN (NEWBORN SGA)

- Due to fetal factors
  - Chromosomopathies (Turner, Down, Prader-Willi, etc.)
  - Syndromic (Silver-Russell, Cornelia de Lange, Noonan, etc)
  - Primordial dwarfism (MOPD I, II, III)
- Due to uterine or placental features
- Due to maternal features
  - Malnutrition
  - Drugs
  - Cardiac pathology
  - Congenital infections (TORCH)

C. PROPORTIONATE OF POSTNATAL ORIGIN

- Malnutrition:
- Chronic infectious diseases
- Organic diseases:
  - Gastrointestinal (celiac disease, Crohn’s disease, cystic fibrosis, short intestine…)
  - Hepatic (biliary atresia, chronic hepatitis, liver transplantation, etc)
  - Renal (glomerular, interstitial, tubular)
  - Cardiac (cianosant congenital cardiopathies)
  - Pulmonar (FQ, asthma, broncopulmonar displasia, apnea obstructiva, secuestro pulmonar…)
  - Metabolic (poorly controlled diabetes mellitus)
  - Hematological (chronic severe anemia, hemochromatosis)
  - Oncological (leukemias, linphomas, tumors of the central nervous system, bone marrow transplantation, etc.)
  - Central nervous system (idiopathic cerebral palsy, myelomenigocele, mental retardation, etc.)
  - Rheumatological (chronic juvenile arthritis, systemic lupus erythematous, etc.)
- Endocrine diseases:
  - GH/IGF-I deficiency or insensitivity
  - Hypothyroidism
  - Hypercortisolism
  - Precocious puberty
  - Pseudohypoparathyroidism
  - Inherited rickets (hypocalcemic and hypophosphatemic)
  - Diabetes mellitus with poor control
  - Diabetes insipidus without treatment
- Psychosocial

II. SHORT STATURE OF UNKNOWN ETIOLOGY: IDIOPATHIC SHORT STATURE

NORMAL VARIANTS OF SHORT STATURE:
- Familial short stature (FSS)
- Constitutional delay of growth and puberty (CDGP)
- Association of FSS and CDGP

OTHER CAUSES YET TO BE KNOWN

A. Isolated GH Deficiency
   ▶ IA (GH1)-AR-
   ▶ IB (GH1, GHRHR)-AR-
   ▶ II (GH1)-AD-
   ▶ III (BTK, SOX3)-X-linked-
   ▶ Ghrelin receptor (GHSR)
   ▶ RNPC3 (minor spliceosome) -AR-
   ▶ Unknown

B. Multiple Pituitary Hormone Deficiency
   ▶ POU1F1-AR, AD-
   ▶ GLI2-AD-
   ▶ PROP1-AR-
   ▶ GLI3-AD-
   ▶ LHX3-AR-
   ▶ FGF8-AD-
   ▶ LHX4-AD-
   ▶ FGF1-AD-
   ▶ HESX1-AR-
   ▶ IGSF1-X-linked-
   ▶ OTX2-AD-
   ▶ RIEG-AD-
   ▶ SOX2-AR-
   ▶ SOX3-X-linked-

C. GH Insensitivity
   ▶ GHR (Laron/Partial) -AR-
   ▶ STAT5b-AR-
   ▶ Bioinactive GH-AR-

D. Primary ALS Deficiency
   ▶ IGFALS-AR-

E. Primary IGF-I Deficiency
   ▶ IGF1-AR-

F. IGF-I resistance
   ▶ IGF1-AR-

G. Primary IGF-II Deficiency
   ▶ IGF2-Paternally Inherited-

H. Primary Protease Deficiency
   ▶ PAPP-A2-AR-

Table II. Known molecular basis of proportionate short stature.
Figure 1. Algorithm for diagnosis of short stature.
Meet the Expert Session
4:1 – 4:2

Use of hormone replacement in females with endocrine disorders

Sophie Christin-Maitre (Paris, France)

Thursday 1 October 16:00 – 17:00 – Hall 7
Saturday 3 October 08:00 – 09:00 – Hall 7
Adele..., 17 yrs. has secondary amenorrhea. Her first menses occurred at the age of 13 yrs., they have been regular every 30 days, during 3 years and stopped at the age of 16. Her weight is 55 kgs and her height 1m 70. Her hormonal levels, checked twice, showed elevated gonadotropins and low estradiol (E2) levels. Her last hormonal evaluation was FSH= 50 IU/L (N: 2-10), LH= 30 IU/L (N: 2-10) and E2= 30 pmol/L (N: 70-120). She never had surgery. She did not receive chemotherapy or radiotherapy. There is no familial history of primary ovarian insufficiency (POI). Her karyotype is 46,XX and no FMR1 premutation has been identified, 21 hydroxylase antibodies are negative. She has been smoking for the past 4 months and is currently smoking 5 cigarettes per day.

What type of hormonal replacement therapy (HRT) can be prescribed to this adolescent? What doses and what route are optimal? What are the goals of this treatment? What follow-up is necessary? For how long should this treatment be prescribed?

Adele has POI and therefore needs HRT containing estrogens in order to compensate her estrogen deficiency. Estrogens can be administered as 17β estradiol (E2), estradiol valerate, conjugated estrogens or ethynyl estradiol (EE). E2 is the endogenous estrogen. In Europe, it is available as a pill, transdermal patches and gel. Estradiol valerate is a synthetic prodrug of 17β estradiol. It is rapidly hydrolyzed to estradiol after oral administration, by intestine enzymes. Conjugated equine estrogens (CEE) are extracted from equine urine and contain more than 100 estrogenic compounds of different potency. The main estrogens contained in CEE are E2, estrone (E1) and estriol (E3). CEE is used mainly in the United States for postmenopausal treatment. Historically, it has been the most widely used form of estrogen for the induction of puberty in the US. EE is a synthetic estrogen, also named 17α estradiol. It was first synthetized in 1938 in Berlin, commercialized in 1943. It is the main estrogen used in combined oral contraceptives (COC). Formulations of COCs have dramatically changed over the past 50 years. EE concentration has decreased, in order to reduce the risk of venous thromboembolism [1]. The most recent contraceptive pill contain 35-15 µg of EE instead of 150-100 µg, in the initial pills. Some COC containing estradiol valerate or 17β-E2 have been available for some years [2].

As our patient has a uterus, progesterone or progestins need to be associated with estrogens, in order to avoid endometrial hyperplasia and potential endometrial carcinoma. Studies performed in postmenopausal women, on hormonal menopausal replacement therapy, have shown that at least 12 days of progestins per month are necessary to avoid the risk of endometrial carcinoma [3]. No data is available so far in young patients on HRT. Natural progesterone can be administered orally or transvaginally. Progestins are synthetic molecules. They can be classified according to their origin, whether they are derived from progesterone or testosterone. They are available as pills, implants and are contained in some intrauterine device (IUD).
Estrogens and progestins can be administered in a separate regimen or can be combined. When estrogens and progestins are prescribed separately, estrogens are usually administered from day 1 to day 25 of the month and progestins from day 12-14 to day 25. In this sequential regimen, no treatment is given between day 25 and the end of the month. Withdrawal bleedings usually occur within few days after stopping the treatment. The main goal of HRT is to substitute estrogen deficiency, therefore to obtain physiological serum levels of E2. In hypogonadal adolescents, daily doses of 2-3 mg of oral E2 or biweekly 50-100 µg E2 patches have been tested. Ethinyl estradiol and conjugated equine estrogen are rarely used nowadays in Europe, as single agent. Orally administered estrogens have hepatic first pass metabolism. This first pass is avoided when estrogen are administered TD. Concerning progesterone dosage, 200 mg of progesterone per day has been tested.

Concerning the route of E2 administration, pharmacokinetics and pharmacodynamics of oral and TD 17 β-E2 have been evaluated mainly in girls and adolescents with Turner syndrome (TS). Taboada et al. recruited 10 girls with TS, mean age 17.7 ± 0.4 (SE) yr and 20 normally menstruating controls [4]. TS were randomized 2 wk. each to oral 0.5 mg and biweekly TD E2 (37.5 µg) with 2 wk. washout in between or oral 2.0 mg and TD E2 (75 µg). E2, estrone (E1) and a recombinant cell bioassay were used. The high dose TD (75 µg) E2 group concentrations were the closest to those of normally menstruating girls. A longer duration of treatment has been evaluated by the same group. Forty girls with TS, with a mean age of 16.7±1.7 years, were randomized to 17 β-E2 orally or 17 β-E2 TD [5]. Doses were titrated using mean E2 concentrations of normally menstruating girls. Mean oral dose was 2 mg and TD dose was 100 µg. The range of doses of E2 is however not mentioned in the paper. Evaluation was performed after 6 months and 12 months on HRT. SHBG level was higher in the oral group, probably due to a higher hepatic effect. Total estrogen exposure was significantly higher after oral 17 β-E2. The potential impact of this higher exposure on the long term remains unknown. This study illustrates that TD 17 β-E2 is more physiologic than oral 17 β-E2.

In the same study, metabolic effects of oral versus transdermal 17 β-E2 have been studied [5]. Changes in body composition and lipid oxidation were evaluated after 6 and 12 months. After 12 months of treatment, the route of delivery of 17 β-E2 did not affect body composition, bone mineral content accrual, lipoprotein profiles, markers of inflammation, blood glucose and insulin concentrations.

Studies performed in postmenopausal women and women with hypopituitarism have raised some concerns about the impact of the oral route of 17 β-E2, on IGF-1 levels. However, Mauras et al. have tested the effects of oral versus TD estrogen, in growth hormone treated girls with TS [6]. Eleven girls, mean age 13.4±0.5 (SE) yr., were randomized and received 17 β-E2 orally (0.5, 1 and 2 mg for 2 wks. each) and 17 β-E2 TD (25, 37.5, 50 µg for 2 wks. each). There was not clinically significant change in IGF1 concentrations after either form of estrogen. Although the duration of each treatment was short, this study illustrates the fact that the route of 17 β-E2 administration does not seem to have a major impact on IGF1 concentrations.

Although TD 17 β-E2 with oral progesterone is probably the most physiological route of HRT, compliance is often an issue. Adolescents often prefer to take a daily pill.

Combined treatments are contraceptive when the progestin contained in the pill has strong antigonadotropic effects. In those combinations, estrogens are present in order to compensate for estrogen deficiency and to regulate vaginal bleedings. However, some combined treatments are not
contraceptive as the progestin contained in the pill is not anti-gonadotropic. Their marketing was initially intended for postmenopausal women.

**The choice between those two treatments should rely on the contraceptive need.** Indeed, although fertility is greatly reduced in patients with POI, studies have shown a rate of spontaneous pregnancies reaching 4-6% [7]. Therefore, when contraception is needed, combined contraception represents the best choice, as implants or IUD, currently available do not contain estrogens. Combined contraception is available as a pill, a patch or a vaginal ring. Obviously, the latest route can only be offered to adolescents with previous sexual activity. COCs are classified into generations, depending on the type of progestin contained in the pill. First generation pill contain norethisterone acetate, lynestrenol, norethynodrel. They are not currently used. The pills available are second, third or new generation pills. Second generation contain norgestrel or levonorgestrel (LNG). Third generation COCs contain dienogest, gestoden or norgestimate. In the past years, some pills have been developed containing “new” progestins, such as drospirenone, chlormadinone acetate [8].

When prescribing a combined contraception, the balance between benefits and risks should be evaluated. First of all, a familial history of venous thromboembolism (VTE) should be sought. As recommended by World Health Organization, when initiating COC, clinical examination should include blood pressure measurement [9]. No gynecological examination is necessary. Many controversies concerning contraceptive pills have risen, especially in France in 2013. All combined oral contraceptives are associated with an increased risk of VTE, however, their absolute risk remains low. VTE risk depends on the estrogen concentration as well as the type of progestin contained in COCP. The thromboembolic risk is higher when EE is higher than 35 µg. It is not statistically different between pills containing less than 35 µg EE. Data on thromboembolic events in women taking pills containing estradiol valerate or 17 Î²-E2 are not available, yet. According to the progestin, the thromboembolic risk reaches 2-4/10 000 women year with pills containing second generation progestins and 4-6/10 000 women year with third generation progestins or new progestins [10]. In other words, VTE risk with 30-35 µg EE and gestodene, desogestrel, cyproterone acetate and drospirenone is similar. It is 50-80% higher than with levonorgestrel [11]. The venous risk with vaginal rings and patches is equivalent to third generation progestins. Lidgaard et al. studied a national danish cohort of women on COCP between 1995 and 2005. In this study, compared to non users, the rate ratio of VTE in current users decreased with duration of use (<1 year 4.17, 95% confidence interval 3.73 to 4.66, 1-4 years 2.98, 2.73 to 3.26, and >4 years 2.76, 2.53 to 3.02; P<0.001) [12]. Those data have been confirmed in a population case-control study from the Netherlands, called MEGA study [13]. This increased risk during the first year, called starter effect, is due to the fact that initiating COCP may reveal coagulation abnormalities, the most frequent ones being Leiden and prothrombin mutations.

Arterial risk, including stroke and myocardial infarction, is extremely low in adolescents and young women. A very recent Cochrane review has included observational studies including women 18-50 years and has compared arterial risk between users and non-users of COC [14]. This network meta-analysis showed that the risk of myocardial infarction or ischemic stroke was only increased in women using COCs containing ≥ 50 µg of EE. Therefore, although our patient is smoking, COC containing 30 µg or less seems safe. According to WHO, the balance between vascular risk and undesired pregnancy should be taken into account.
Furthermore, when choosing the type of HRT, non-contraceptive benefits of the COCs should be taken into account. For instance, if the adolescent does not wish to have menses on a monthly basis, extended regimens can be advised [15]. In such cases, pills are given continuously for 3-6 months. A duration longer than 6 months usually induces spotting. Among the non-contraceptive benefits, most COCs decrease menstrual flow and reduce dysmenorrhea [16].

What are the goals of HRT in our patient?

The goals of HRT in adolescents are to develop and maintain secondary sexual characteristics, mainly breast development, feminization, induce growth spurt and maintain bone mass.

HRT decreases hot flushes although they are not always present in young patients with POI. If the patient is symptomatic on sequential treatment, a continuous regimen can be prescribed, in order to avoid hot flushes and night sweat. HRT has an impact on endometrial thickness, uterine perfusion but this impact is mainly required during oocyte donation programs.

Bone health represents a major issue for this adolescent. Research has shown that the highest velocity of bone mass accrual occurs 1 year before menarche and after the first 3 years [17]. POI has been shown to be associated with decreased bone health, especially in the first years after diagnosis [18]. Although no data is available on the risk of fractures, estrogen treatment should be given in order to reduce the risk of osteoporosis, essentially in the spine region which is very sensitive to estrogens.

Furthermore, HRT protects against cardiovascular risk. Epidemiological studies performed in the Netherlands, have shown that estrogen deficiency, before the age of 40 is related to an increased cardiovascular risk [19]. In the Mayo Clinic cohort, increased mortality was seen mainly in women who had not taken estrogens up to the age of 45 years. Although both treatment contain estrogens and progestins, HRT’s cardiovascular effects in young patients should be distinguished from cardiovascular impacts described in postmenopausal women taking menopausal treatment. This illustrates the “timing theory of estrogens”. They are beneficial in young patients and deleterious in women with atherosclerosis [20].

The effects of HRT on cognitive function, after long term use in adolescents with POI, is currently not known. Data are only available in women who had bilateral oophorectomy before the age of natural menopause. Estrogen deficiency occurring too soon in those women is associated with an increased prevalence of dementia.

In the literature, so far, only one case with ERS1 receptor mutation has been reported in a female. This 18 year old patient presented at the age of 15 with primary amenorrhea and Tanner stage 1 breast development. Her estradiol plasmatic level of E2 reached 3500 pg/ml (N: 11-210). Estradiol resistance was confirmed as a loss of function mutation of estrogen receptor (ERS1) was identified. She lacked an estrogen-induced growth spurt at time of puberty. At 17 years and 5 months, her Z score of total bone density was -2.4 SD. Data on long term effects of her estrogen deficiency, are not available, as the patient is still too young [21].

The duration of HRT is recommended up to the age of physiological menopause, on average 50-51 yrs.
Follow-up of POI patients on HRT, can be proposed, once a year. The main goal of each visit is to check about compliance. In the follow-up of POI patients on HRT, estradiol or FSH monitoring is not helpful.

Several studies have evaluated the risk of breast cancer in women with POI. Wu et al. have shown a decreased risk [22]. Furthermore, Bosze et al. have followed women with POI during 40 years. The risk of breast cancer is not increased in women taking HRT, before the natural age of menopause [23]. Therefore, mammography or breast ultrasound should not be performed on a routine basis, before the age of 45. They should be performed earlier, only in patients with familial cases of breast cancer diagnosed before the age of 50, in at least 2 first degree relatives.

Bone evaluation by Dual Energy X-ray Absorptiometry (DEXA) can be recommended when the diagnosis of POI is performed and every 5 years, in young patients. DEXA can be used to evaluate HRT compliance. As our patient is smoking, she should definitely be advised to stop smoking, as tobacco alters bone density.

If our patient was 17 but had no breast development and primary amenorrhea, the goal of HRT would be initially to induce breast development. Guidelines have been established [24]. Estrogens should be administered initially alone, and the dosage increased progressively, in order to mimic natural puberty. The preferred route of administration is transdermal and the type of estrogen 17β estradiol. CEE or combined COC are not currently recommended to induce breast development as estrogen concentration is probably too high. When starting estrogen, at the age of 12 years, the recommended dose is one tenth to one eighth of the adult replacement dose. However, if the treatment is started at age 17, the initial dose of estrogen can be higher, between 0.5 to 1 mg of 17β estradiol. In theory, progestins should be administered, at least 2 years after beginning the estrogens or when spotting occurs. In adolescents, progestins can be added after one year after starting estrogen, instead of two. This is however based on expert practice and not on randomized studies.

When the diagnosis of hypogonadism is performed in childhood, the optimal age to start has been a subject of controversy, between 12, 13 or higher. International guidelines actually recommends starting estrogen at the age of 12. When starting E2 around the age of 12, initial dose of estrogen is 0.08–0.12 μg/kg. TD E2 is preferred. The patch is placed on the superior lateral glutea in the evening at bedtime and removed the following morning, resulting in approximately 10 h of treatment. Within 1–2 weeks of the start of treatment, physicians are recommended to monitor the morning serum E2 with the patch still in situ, in order to adjust the dose if the target E2 range is not reached. However, earlier treatments have been suggested by Ross et al. This group suggests starting estrogens in Turner syndrome patients as early as 5 years [25, 26]. Childhood low-dose estrogen replacement seems to normalize the onset and the tempo of puberty.

In conclusion, when treating a girl with hypogonadism, the optimal estrogen route, drug, dose have to be adjusted for every patient. In order to decide which type of treatments should be prescribed, one should take into account the patient’s preference for combined or separate regimen, the need for contraception and the preferred frequency of breaktrough bleedings. Although 1 in 4 adolescent females will be exposed to hormonal contraceptive by the age of 18, pediatric pharmaceutical testing of COCP is lacking. For instance, solid data about the impact of different COCPs on peak bone mass acquisition are lacking. So far, most studies available on HRT in young patients have included
patients with Turner syndrome. Therefore, studies on HRT are necessary in other causes of POI as well as in patients with hypogonadotrophic hypogonadism.

References


[9] World Health Organization Selected practice recommandations for contraceptive use 3rd edition reproductivehealth@who.int


Meet the Expert Session
5:1 – 5:2

Management of the adolescent with CAH

Peter Hindmarsh (London, UK)

Friday 2 October 08:00 – 09:00 – Hall 5
Saturday 3 October 15:30 – 16:30 – Hall 5
Mini review

The Importance of Absorption and Clearance in determining Hydrocortisone Replacement in Children and Young People with Congenital Adrenal Hyperplasia

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Developmental Endocrinology Research Group, UCL Institute of Child Health, London, United Kingdom

Presentation at the 54th Annual Meeting of the European Society for Paediatric Endocrinology, Barcelona, 2015
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The treatment of congenital adrenal hyperplasia (CAH) requires administration of glucocorticoid and mineralocorticoid to replace the deficit resulting from the enzymatic block. 24 hour profiles along with assessment of Hydrocortisone clearance is vital when calculating and/or titrating dosing schedules for individuals as the half-life of cortisol is very variable ranging between 40 and 225 minutes. This variation may be intrinsic to the individual (permanent) or secondary to changes in cortisol metabolism during puberty (transient). Before assuming that poor control of CAH represents lack of compliance attention must be paid to the pharmacology of Hydrocortisone. Cortisol replacement should not be judged solely on 17 OHP. Fast clearers will require an increase in dosing frequency and if this proves problematic continuous subcutaneous Hydrocortisone delivery using insulin pump technology is valuable.
INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency is an autosomal recessive condition, in which deletions or mutations of the cytochrome P450 21-hydroxylase gene result in glucocorticoid and mineralocorticoid deficiency. This leads to increased secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary, adrenal hyperplasia, accumulation of steroid precursors prior to the enzymatic defect and increased production of androgens (1). Glucocorticoid therapy substitutes the missing cortisol and this in turn suppresses the excessive secretion of corticotrophin releasing hormone (CRH) and ACTH, reducing the circulating concentrations of androgens. Replacement therapy is conventionally assessed retrospectively by monitoring annualised height velocity and the rate of skeletal maturation and prospectively by 24 hour profiles of adrenal steroids.

Despite adequate substitution therapy control of CAH is often difficult. Limitations of current medical therapy include the pharmacology of Hydrocortisone, the inability to control hyperandrogenism without inducing hypercortisolism, the lack of appreciation of the circadian rhythm of cortisol and the feedback systems (2, 3). Many clinical observations suggest that puberty is associated with difficulty in achieving and maintaining adrenal suppression, despite optimal doses of substitution therapy. This has been attributed traditionally to non-adherence as a result of psychosocial factors relating to adolescence. This may not be the case for two reasons. First, patients may metabolise hydrocortisone differently throughout life so loss of control during puberty is simply an exacerbation of this problem, permanent metabolic instability. Second, alterations in the endocrine milieu at puberty may influence cortisol pharmacokinetics and consequently, the handling of hydrocortisone, a transient metabolic instability.

In addressing loss of control in CAH it is important to understand the physiology of cortisol secretion and also the pharmacology of Hydrocortisone.
CIRCADIAN RHYTHM OF CORTISOL

The daily cortisol production rate is remarkably constant at all ages but the amount of cortisol that can be measured in the blood varies during the 24 hour period - the circadian rhythm. The rhythm reflects changes in the amount of CRH and ACTH produced during the 24 hour period and mirrors hypothalamic clock activity. Cortisol is one mechanism whereby synchrony is maintained between the central and peripheral clocks (4). Figure 1 shows this rhythm with the highest cortisol concentrations occurring in the early hours of the morning and a surge of ACTH driven cortisol at 16.00h. It is not until mid-evening that concentrations become low but are always measurable.

Figure 1. The circadian rhythm of cortisol. Plasma cortisol begins to rise from a nadir at midnight to reach peak concentrations between 07:00 and 09:00h. Concentrations gradually decline during the day to 16:00h where there is an ACTH driven peak. Note that at all times even at the nadir cortisol is always measurable in the blood.
One of the tenants of endocrinology is to replace hormones that are missing as close to physiology as possible. Considering the wide ranging effects of cortisol in the body this is particularly important as both over and under replacement is detrimental.

The circadian rhythm is remarkably similar at different ages and between the sexes. Mean daily cortisol secretion is similar between adults (6.3 mg/m$^2$ body surface area/day, range 5.1-9.3) and children (8.0 mg/m$^2$ body surface area/day, range 5.3-12.0). The timing of the peak serum cortisol concentration is also similar (07:00-09:00h), whereas the nadir concentration occurs later in adults (midnight) compared to children (22:30h) which reflects differences in bedtimes.

Cortisol concentration profiles can be analysed using deconvolution analysis to determine the total amount of cortisol secreted per day and its distribution over 24 hours (3). These observations suggest that the daily Hydrocortisone replacement dose should be equivalent on average to 6-7 mg/m$^2$ body surface area/day in adults and in children 8.0 mg/m$^2$ body surface area/day values which are consistent with stable isotope studies. Such analysis does not take into account two additional points. First, the entero-hepatic circulation of steroids which is important for oral replacement therapy (5) and second, slightly more cortisol will be required to suppress ACTH in CAH when the adrenals are large. This is certainly the case with oral therapy whilst on pump therapy cortisol replacement is the same as the normal daily production rate. Taking this into account the amount of Hydrocortisone required is approximately 10-12 mg/m$^2$ body surface area/day.

Hydrocortisone lasts in the circulation on average for 6 hours so the most logical dosing schedule is four times per day rather than the current three times per day regimen. If we dose four times per day in order to match the different amounts of cortisol normally secreted during the 24 hour period we would need to distribute the Hydrocortisone as in Table 1.
TABLE 1. Percentage of Total Daily Cortisol Made by the Adrenal Gland at Different Times of the Day in Children

<table>
<thead>
<tr>
<th>Time Segment</th>
<th>Percentage of Total Cortisol Secretion during Time Segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>06:00 – 12:00</td>
<td>38.4</td>
</tr>
<tr>
<td>12:00 – 18:00</td>
<td>21.2</td>
</tr>
<tr>
<td>18:00 – 24:00</td>
<td>10.7</td>
</tr>
<tr>
<td>24:00 – 06:00</td>
<td>29.7</td>
</tr>
</tbody>
</table>

PHARMACOLOGY OF HYDROCORTISONE

In addition to knowing the total dose of Hydrocortisone required and how it is to be distributed through the 24 hours we also need to understand how Hydrocortisone is absorbed and cleared from the blood. The bioavailability of Hydrocortisone is quite high at 80-95%. The speed at which it enters the circulation is variable as it depends on gut motility, whether the drug is taken with food and potential metabolism by bacteria in the gut.
Clearance of cortisol from the circulation can be measured by an intravenous bolus administration of Hydrocortisone. Absorption can be determined from a series of pharmacological parameters, such as the maximum concentration attained ($C_{\text{max}}$) and the time to peak concentration ($t_{\text{max}}$) (6, 7).

Differences in the absorption of oral Hydrocortisone exist between individuals with a wide range in $t_{\text{max}}$ (range 20 to 118 min) (8). This explains why some individuals display good control, based on 17OHP measures only, on a twice daily regimen using two high doses and why it has been difficult to demonstrate superiority of multiple dosing regimens.

The mean half-life of Hydrocortisone is 76.5 min with a wide range (40 to 225.3 min). This means that there are individuals who are fast absorbers and either slow or fast clearers and others that are slow absorbers and fast or slow clearers with a host of other variations in between. We are only beginning to understand how this works in clinical practice by describing parameters such as terminal half-life which is an attempt to unify these concepts into a single value (9). A simple way is to think of how quickly or slowly a person attains a cortisol concentration less than 100 nmol/l after ingestion of Hydrocortisone. Individuals where the half-life is fast and the $t_{\text{max}}$ is obtained quickly have the shortest time to attain a plasma cortisol concentration of less than 100 nmol/l (240 minutes). If the $t_{\text{max}}$ is prolonged the effect of the fast half-life can be ameliorated (380 minutes).

These considerations need to be placed in the context of other factors modulating glucocorticoid availability and action. Cortisol binding globulin (CBG) will modify the total amount of cortisol in the circulation. The dynamics of how much cortisol is bound to CBG and albumin depends upon the circulating cortisol concentration and body temperature. Medications such as the oral contraceptive pill, aromatase inhibitors and thyroxine will alter cortisol dynamics, altering Hydrocortisone dosing.
PERMANENT AND TRANSIENT ALTERATIONS TO HYDROCORTISONE CLEARANCE

There are two, not mutually exclusive, explanations for the changes in cortisol clearance in puberty that have been documented. It is important to recognise that the studies on cortisol clearance are cross sectional in nature so it is possible that there are individuals in the study populations that have long standing or permanent problems in how they handle cortisol. Given the complexity of the metabolism of cortisol it would not be surprising that some individuals handle cortisol differently either as fast or slow clearers. This problem would be permanent and exacerbated by changes during puberty. Another group might represent a more transient population who only have problems on fixed doses of Hydrocortisone when pubertal changes take place and settle once the hormonal disturbance of puberty calms. Studies have shown a significant increase in cortisol clearance at puberty and a shorter half-life of cortisol in pubertal females compared to their male counterparts (7) with a wide range in the half-life in patients with CAH. We only understand part of this and this section will consider the impact of hormonal changes during puberty on cortisol metabolism.

Puberty results from increased gonadotrophin secretion from the anterior pituitary in response to gonadotrophin releasing hormone (GnRH) secretion from the hypothalamus. The rise in sex steroid concentration is associated with increased growth hormone (GH) secretion from the anterior pituitary, which leads to increased insulin-like growth factor (IGF)-I concentration and the pubertal growth spurt. Associated with this there is a decrease in insulin sensitivity and a parallel elevation in insulin concentrations.

The increase in cortisol clearance at puberty seems to arise from the inhibition of the activity of 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) secondary to alterations in the endocrine milieu. 11beta-HSD1 acts as an oxo-reductase, converting inactive cortisone to active cortisol. The increase in GH, IGF-I, and estradiol concentrations at puberty lead to a decrease in the activity of
11beta-HSD1. The effect of IGF-I on 11beta-HSD1 activity is further enhanced by the decrease in IGFBP-1 concentration secondary to the raised insulin concentration. Inhibition of 11beta-HSD1 activity effectively increases the metabolic clearance rate of cortisol. GH and IGF-I also increase glomerular filtration rate increasing cortisol clearance (10).

The changes in cortisol pharmacokinetics, in the presence of a fixed Hydrocortisone dosing schedule will result in hypocortisolism and reduced feedback inhibition on CRH and ACTH with increased production of androgens and steroid precursors. The increased secretion of adrenal androgens will be amplified by increased 17, 20 lyase activity and/or decreased 3beta-hydroxysteroid dehydrogenase activity secondary to the rise in GH, IGF-I, IGF-II, and insulin concentrations at puberty. Moreover, the increased insulin concentrations will suppress the synthesis of sex hormone binding globulin by the liver, further enhancing hyperandrogenism. As androgens and androgen precursors are known to compete with exogenously administered glucocorticoids for the same receptors, both hypocortisolism and hyperandrogenism will operate as independent factors to amplify the loss of control. Increased ACTH secretion, in turn, may further potentiate hypocortisolism by increasing the metabolic clearance rate of cortisol. Finally, estradiol will lead to an increase in CBG so that although total cortisol may increase the free component will decrease. This may explain why cortisol clearance is faster in females than males.

MONITORING THERAPY

A variety of ways have been proposed to monitor replacement therapy in CAH. Many have focused on markers such as 17 hydroxypregesterone (17OHP). Measurements have ranged from urine tests, salivary steroid estimation and blood spots. Figure 1 tells us that unless careful attention is paid to sampling then false conclusions may be drawn.
If sampling is undertaken infrequently then peaks and troughs may not be estimated correctly, a phenomenon known as aliasing. If the half-life of a hormone is known then this tells us the minimum period of time for sampling. Sampling intervals greater than the half-life will lead to underestimations of what is actually happening. Taking a blood sample before and 2 hours after ingestion of Hydrocortisone will not tell us about important parameters such as how long does the drug last and how long is the person without Hydrocortisone. It will not even give information on the actual peak as the average $t_{\text{max}}$ is 60 – 80 minutes nor when to stack or not to stack. Cortisol stacking is the phenomenon that occurs if doses are given close to each other where the second dose adds onto the first leading to higher cortisol exposure. This can be unhelpful at times leading to over treatment but can be used for benefit if Hydrocortisone is given as the cortisol concentration wanes thereby boosting the concentration, prolonging exposure and avoiding periods of under exposure. You can only work this out from 24 hour profiles.

It is important to think about what we are doing in CAH replacement therapy. Following our endocrine tenant on hormone replacement we can say that in CAH what is missing is cortisol, what we are replacing is cortisol using Hydrocortisone and we need to know first and foremost how the cortisol replacement looks. Placing cortisol at centre-stage may seem at odds with conventional thinking where 17OHP has been the main player. However, it is time to rethink this and put cortisol to the fore. First, we are replacing with cortisol and if we get cortisol right then the feedback loop will ensure that all other parameters will follow. Second, all the side effects that we wish to avoid relate predominantly to over or under treatment with cortisol. Over treatment is particularly important to avoid with respect to the CAH Metabolic Syndrome. Third, reliance on 17OHP or androstenedione assumes that the dose response curves for the switch off of these steroids are the same as the normal amount of cortisol in the circulation. This is in fact not the case as the average mean 24 hour cortisol concentration is 300 nmol/l whereas the amount needed to switch off 17OHP or androstenedione is about 150 nmol/l. This means that using these parameters the patient would have “good control” but
still suffer cortisol deficiency symptoms which may lead to side-effects such as adrenal rests in the testes and ovaries. Finally, time lags exist in the system. When cortisol changes, 17OHP does not immediately follow suit. There is a time lag of anything between 1 and 2 hours, so interpreting and changing Hydrocortisone doses solely on 17OHP can be erroneous as this might lead to overtreatment or suggest non compliance.

At our Hospitals we use 24 hour cortisol and 17OHP profiles obtained by sampling every 1-2 hours. This allows us to see exactly what is happening with replacement therapy. We want to know if the cortisol distribution is optimal over the 24 hour period, are the cortisol peaks too high or too low and occurring at the right times of the day, is the dose providing adequate cortisol cover, is over stacking occurring, and finally what effect is the cortisol having on the 17 OHP?

Profiles such as the one shown in Figure 2 allow us to answer these questions.

**Figure 2.** The circadian rhythm that we are trying to mimic is shown by the dashed line. The plasma cortisol concentration from the thrice hydrocortisone doses is shown as shaded areas. The actual 17 hydroxyprogesterone attained is the purple line linking the triangles. A one off 17OHP measurement is shown by the orange square and a series by the green squares. Note how the 17OHP can suggest good control yet there are periods of time when the person is cortisol deficient for 40% of the time.
By carefully considering these questions and by understanding the issues of absorption and clearance, we are able to better tailor what starts as a conventional dosing schedule to the actual needs of the patient. Using this approach we have found that a four times per day Hydrocortisone regimen is the optimal approach. We have also made equal number of changes to dose and frequency on the basis of profiles reducing our patients’ exposure to high doses of Hydrocortisone and at the same time reducing body mass index (Table 2.)
TABLE 2. Changes in Hydrocortisone Dosing and Body Mass Index Over a 12 Year Period

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocortisone Dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mg/m²/day)</td>
<td>17.5</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td>1.57</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**MANAGING PATIENTS WITH A FAST CLEARANCE**

Patients with a fast clearance or short half-life need Hydrocortisone treatment that is given frequently. Simply increasing the dose will not make any difference because no matter how high the dose it will not last in the circulation very much longer unless excessively high doses are given. This is because of the maths of half-life and the exponential way that cortisol concentrations decline with time. To manage these situations Hydrocortisone needs to be given more frequently and an estimate can be derived from the half-life. Roughly the duration of exposure to the drug will be 3-4 times the half-life. So if the half-life is 40 minutes then the Hydrocortisone would need to be given every 180-240 minutes. In fact as the concentration at the end of this time period would be zero then in order to avoid this even more frequent administration would be required.

Another way to improve the situation is to deliver the Hydrocortisone using insulin pump technology (11). This is a useful approach as in order to overcome the rapid clearance of hydrocortisone, a high frequency of oral hydrocortisone dosing is required which is impractical and may not achieve adequate control. Introduction of hydrocortisone using an insulin pump can normalise all the control
measures of CAH, namely 17OHP and androstenedione, as well as delivering a physiological circadian rhythm of cortisol in the circulation.

Mimicking the circadian rhythm leads to plasma 17OHP concentrations within the normal range. When giving Hydrocortisone orally is has often been argued by clinicians that any 17OHP concentration within the normal range may represent over treatment. The pump delivery of Hydrocortisone and the normalisation of 17OHP which occurs at the same time as the delivery of a normal plasma cortisol concentration argues against this in this situation. Normalisation of 17OHP concentrations using Hydrocortisone pump therapy is achieved without excessive exposure to cortisol. Where pump therapy really works well is that the infusion can be altered to match the circadian rhythm exactly and abolish the early morning surge in 17OHP which is almost impossible to blunt with conventional oral therapy without over treatment (12).

Pump therapy is particularly valuable for individuals who have rapid clearance of cortisol from the circulation and in whom adequate cortisol concentrations cannot be achieved using conventional or up to 4 to 5 times per day oral replacement therapy. Patients with severe gastritis secondary to previous oral glucocorticoids can also benefit by by-passing the abnormal absorption. Pubertal individuals who have a transient increase in the rate of cortisol metabolism and in whom re-establishing control remains challenging and those patients requiring high dose glucocorticoid therapy for control and who are developing side effects such as obesity or hypertension are also candidates for pump therapy.

CONCLUSIONS

The dose and frequency of Hydrocortisone administration may need to be altered in individuals depending on the half-life of cortisol in the circulation and the absorption of oral Hydrocortisone from the gastrointestinal tract. More detailed individualised pharmacokinetic parameters now need to be
devised in order to better prescribe the dosing schedules that should be undertaken in order to mimic the physiology of cortisol secretion in people with CAH. A four times a day regimen would appear to be the right one to adopt to provide better cortisol distribution. This may change during puberty or the introduction of oral contraceptive therapy, which means reassessment of the pharmacokinetic parameters. These observations highlight the importance of detailed profiling of plasma cortisol concentrations arising from Hydrocortisone administration.
REFERENCES


Meet the Expert Session
6:1 – 6:2
Management of Prader-Willi syndrome in toddlers

Maithé Tauber (Toulouse, France)

Friday 2 October 08:00 – 09:00 – Hall 3
Saturday 3 October 15:30 – 16:30 – Hall 7
Meet the Expert Session
7:1 – 7:2
Management of late-effects in the child/adolescent with cancer
Charles A Sklar (New York, USA)

Friday 2 October 08:00 – 09:00 – Hall 4
Saturday 3 October 08:00 – 09:00 – Hall 7
Meet The Expert: Management of Late Endocrine Effects in the Child/Adolescent with Cancer

Charles Sklar, MD
Memorial Sloan Kettering Cancer Center
New York, NY

DISCLOSURE STATEMENT

Speakers Name: Charles Sklar

✓ I have the following potential conflicts of interest to report:

- Research Contracts
- Consulting
- Employment in the Industry
- Stockholder of a healthcare company
- Owner of a healthcare company
✓ Other(s)—Honourarium from Sandoz

☐ I declare that I have no potential conflict of interest.
ALiCCS: Cumulative risk for a first hospital contact for an endocrine disorder (n=31,723)

- Relative risk of endocrine diagnosis was 4.8 (4.8-5.0 95%CI) in survivors compared to controls.
- The prevalence of endocrine disease by the age of 60 years was 43% in individuals diagnosed with cancer when they were 5-9 years old.


Risk of Endocrine Complication by Cancer Diagnosis

Risk of Endocrine Complication by Cancer Diagnosis

[Bar chart showing risk of endocrine complications by cancer type, with labels such as Leukemia, Hodgkin's lymphoma, Non-Hodgkin lymphoma, and others.]

*de Fine Licht S. et al. Lancet, 2014;3;1981*

Risk Factors for Late Effects: Therapeutic Exposures

[Venn diagram showing overlap between Chemotherapy, Radiation, and Surgery.]
Radiation-induced abnormalities are, in general, both dose- and time-dependent

Factors to be Considered in Risk of Late Effects
Childhood Cancer Survivor Study (U24 CA55727)

- Funded in 1994
- Retrospective Cohort, diagnosed 1970-1999
- 31 Contributing Centers
- 5-Year Survival
- Leukemia, Lymphoma, CNS, Bone, Wilms, NBL, Soft-tissue sarcoma
- Detailed Treatment Data, Wide Range of Outcomes

<table>
<thead>
<tr>
<th>Eligible</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>35,923</td>
<td>24,368</td>
</tr>
<tr>
<td>20,690 (1970-86)</td>
<td>14,364 (1970-86)</td>
</tr>
</tbody>
</table>

Children’s Oncology Group Guidelines for Follow-Up of Survivors

http://www.survivorshipguidelines.org/
Case 1: S/P Multimodality Therapy for Standard-Risk Medulloblastoma

- Age at diagnosis: **4 10/12 yrs**
- Age at completion of therapy: 6 yrs
- Age at referral: **7 yrs**
- Reason for referral: Endocrine follow-up
- Family and Past Medical History: Unremarkable
- Treatment:
  - Surgery
    - GTR of posterior fossa tumor
  - Chemotherapy
    - cisplatin, vincristine, lomustine (CCNU)
  - Radiation
    - 2340 cGy whole brain/spine; 3240 cGy boost to tumor bed (total dose to tumor bed 5540 cGy) IMRT
      - estimated dose to HPA ~3800 cGy
      - estimated dose to thyroid ~1630 cGy
Fig. 6 (a, b) Medulloblastoma, composite of craniospinal plus posterior fossa: Dose-volume histogram comparisons across treatment modalities. (EB = electron beam.)
Case 1:  ♀ S/P Multimodality Therapy for Standard-Risk Medulloblastoma

- Initial visit: age 7 yrs
  - HPI: Doing well, active, extra-support in school
  - PE: WDWN, Height 18th percentile; Sitting height - 2 SD; Weight 23rd percentile; BMI 60th percentile.

- Keeping in mind her age and prior cancer treatment:
  - What other physical findings would you want to know?
    - Normal thyroid without palpable nodules; prepubertal exam
  - For which endocrine, reproductive, metabolic abnormalities is she at risk?
    - Neuroendocrine: GHD, precocious puberty, LH/FSH, ACTH, TSHD (HPA RT)
    - Thyroid: Hypothyroidism, thyroid neoplasms (C51)
    - Gonadal: Premature ovarian insufficiency, impaired fertility (C51, CCNU)
    - Metabolic syndrome (CRT)

Threshold Dose of RT for Clinical Neuroendocrine Dysfunction

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Radiation Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH deficiency</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>LH/FSH deficiency</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>TSH deficiency</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>ACTH deficiency</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>&gt; 40-50</td>
</tr>
</tbody>
</table>
Cumulative Incidence of Hypothyroidism in the CCSS

Hypothyroidism

Cumulative incidence (%) vs Years since primary cancer diagnosis.

Mostoufi-Moab S et al, 2015

Cumulative Incidence of Hypothyroidism in the CCSS

Underactive Thyroid

Cumulative incidence (%) vs Years since primary cancer diagnosis.

Mostoufi-Moab S et al, 2015
Case 1: ♀ S/P Multimodality Therapy for Standard-Risk Medulloblastoma

• What screening endocrine studies would you order at this visit?
  – TSH 3.2 (0.5-4.9)
  – Free T4 0.9 (0.9-1.8)
  – 0800 cortisol 15.3 mcg/dL (422.1 nmol/L)

• Started on thyroid hormone replacement
  • Recheck TFTS in ~ 6 weeks, return visit in 6 months

Case 1: ♀ S/P Multimodality Therapy for Standard-Risk Medulloblastoma

• Follow-up visit 7 months later
  – PE: growth velocity 2.8 cm/yr, Height 10th percentile, Sitting height - 2 SD; Weight 35th percentile; Tanner I B and P.H.
  – Given her poor linear growth, what studies would you order?
  • TSH 2.5 (0.5-4.9)
  • Free T4 1.4 (0.9-1.8)
  • CBC, metabolic panel; both normal
  • Bone age 5 y/o yrs (CA 7/12 yrs)
  • GH stimulation with Arg & Clonidine
    – Peak GH 7.5 ng/ml (>10)
    – IGF-1 96 ng/ml (76-424)
Pitfalls in the Diagnosis of Radiation-Induced GHD

- Both IGF-1 and IGFBP-3 poor predictors of RT-induced GHD
  - False negatives common
- GH response stimulus-dependent
  - ITT appears most sensitive
  - GHRH-Arginine cannot reliably exclude GHD, especially in first 5-10 yrs post RT
- Neurosecretory dysfunction
  - Normal response to stim testing but endogenous production low

Case 1: ♀ S/P Multimodality Therapy for Standard-Risk Medulloblastoma

- Given her diagnosis of GH deficiency:
  - What do you tell the family regarding risks and benefits of GH replacement?
    - Risks for established adverse events (eg, SCFE, pseudotumor, type 2 DM)?
      - Probably similar to idiopathic GHD
    - Risk of recurrence of medulloblastoma?
      - Same as survivors not treated with GH
GH Therapy and Tumor Recurrence: Malignant Diseases

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tumor Type (n)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swerdlov et al, 2000</td>
<td>CNS (180)</td>
<td>0.5 (0.4-0.9)</td>
</tr>
<tr>
<td>Packer et al, 2001</td>
<td>Medulloblastoma (170)</td>
<td>0.7 (0.5-4.3)</td>
</tr>
<tr>
<td>Sklar et al, 2001</td>
<td>CNS (172) Acute Leukemia (122)</td>
<td>0.3 (0.3-0.8)</td>
</tr>
<tr>
<td></td>
<td>Rhabdomyosarcoma (39)</td>
<td>0.8 (0.1-6.1)</td>
</tr>
<tr>
<td></td>
<td>Neuroblastoma (17)</td>
<td>0.0</td>
</tr>
<tr>
<td>Leung et al, 2002</td>
<td>Acute Leukemia (47)</td>
<td>No recurrences</td>
</tr>
<tr>
<td>Sanders et al, 2005</td>
<td>Stem Cell Transplant (42)</td>
<td>Not different</td>
</tr>
<tr>
<td>Mackenzie et al, 2011</td>
<td>CNS (110)</td>
<td>Not different</td>
</tr>
</tbody>
</table>

Case 1: ♀ S/P Multimodality Therapy for Standard-Risk Medulloblastoma

- Given her diagnosis of GH deficiency:
  - What do you tell the family regarding risks and benefits?
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Case 1: S/P Multimodality Therapy for Standard-Risk Medulloblastoma

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      - Same as survivors not treated with GH
    - Risk of second neoplasm?
      - Possible small increased risk of secondary non-CNS neoplasms compared to survivors not treated with GH

GH and Risk of Subsequent Neoplasm

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Agent</th>
<th>RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Leung et al, 2001</td>
<td>47</td>
<td>rhGH</td>
<td>4.3% vs 2.9%</td>
</tr>
<tr>
<td>*Sklar et al, 2002</td>
<td>361</td>
<td>pitGH and rhGH</td>
<td>5.22 (1.68 - 5.46)</td>
</tr>
<tr>
<td>*Ergun-Longmire et al, 2006</td>
<td>361</td>
<td>pitGH and rhGH</td>
<td>2.15 (1.3 - 3.5)</td>
</tr>
<tr>
<td>Mackenzie et al, 2011</td>
<td>110</td>
<td>rhGH</td>
<td>4.5% vs 2.7%</td>
</tr>
</tbody>
</table>

* Childhood Cancer Survivor Study
### Second Neoplasms in GH-Treated Survivors

#### Original CCSS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SN</th>
<th>Original</th>
<th>Updated</th>
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<tbody>
<tr>
<td>Acute leukemia</td>
<td>Osteogenic sarcoma</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Astroglial CNS tumor</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Meningioma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CNS tumor</td>
<td>Meningioma</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Carcinomas</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>(parotid, colon, thyroid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Sarcomas</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(spindle cell, tongue)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Astroglial CNS tumor</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
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#### Updated CCSS

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<th>Diagnosis</th>
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<th>Original</th>
<th>Updated</th>
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<td>Acute leukemia</td>
<td>Osteogenic sarcoma</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Astroglial CNS tumor</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Meningioma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CNS tumor</td>
<td>Meningioma</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Carcinomas</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
<td></td>
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</table>
Risk of Second CNS Neoplasms in GH Treated Survivors Stratified by Radiation Dose to CNS

<table>
<thead>
<tr>
<th>Prior cranial radiation ≤45 Gy</th>
<th>Meningioma RR (95% CI)</th>
<th>P Value</th>
<th>Gloma RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No GH treatment (n = 376)</td>
<td>1.0 (0.2-3.5)</td>
<td>.8</td>
<td>1.1 (0.1-8.4)</td>
<td>.93</td>
</tr>
<tr>
<td>GH treatment (n = 131)</td>
<td>1.0 (0.2-3.5)</td>
<td>.51</td>
<td>1.0 (0.1-8.4)</td>
<td>.23</td>
</tr>
</tbody>
</table>

* Adjusted for age at the follow-up, sex, age at primary diagnosis, CRRtime since CRT radiation (time dependent), intrathecal methotrexate, estrogen and/or progesterone treatment (time dependent), and alkylating agents (yes/no). GH treatment is the time-dependent variable.

Patterson et al, J Clin Endocrinol Metab 2014;99:2030

Case 1: ♀ S/P Multimodality Therapy for Standard-Risk Medulloblastoma

- Given her diagnosis of GH deficiency:
  - What do you tell the family regarding risks and benefits?
    - Risks for established adverse events (eg, SCFE, pseudotumor, type 2 DM)?
      - Probably similar to idiopathic GHD
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    - Expected growth response to GH?
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      - Same as survivors not treated with GH
    - Risk of second neoplasm?
      - Possible small increased risk of secondary non-CNS cancers compared to survivors not treated with GH
    - Expected growth response to GH?
      - Suboptimal due to prior spinal radiation at young age

Factors Associated with Improved Height SDS on GH (n=183)

- Young age/bone age at start
- Dose of GH
  - >0.3 mg/kg/wk better than 0.25-0.3 mg/kg/wk better than <0.25 mg/kg/wk
- Male sex
- Spine RT < 20 Gy

Brownstein et al, JCEM 89:4422, 2004

Final height standard deviation score (SDS) after GH therapy according to original diagnosis and exposure to direct spinal radiation therapy (RT)

Brownstein et al, JCEM 89:4422, 2004
Case 1: *S/P Multimodality Therapy for Standard-Risk Medulloblastoma*

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    - Expected growth response to GH?
      - Suboptimal due to prior spinal radiation
    - When is it safe to start GH therapy?
Case 1: ♀ S/P Multimodality Therapy for Standard-Risk Medulloblastoma

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      — Possible small increased risk of secondary non-CNS neoplasms compared to survivors not treated with GH
    • Expected growth response to GH?
      — Suboptimal due to prior spinal radiation
    • When is it safe to start GH therapy?
      — >/= 1 Yr disease-free, off all cancer therapy

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    • Expected growth response to GH?
      — Suboptimal due to prior spinal radiation
    • When is it safe to start GH therapy?
      — >/= 1 Yr disease-free, off all cancer therapy
    • What dose of GH would you use?
Case 1: S/P Multimodality Therapy for Standard-Risk Medulloblastoma

- Given her diagnosis of GH deficiency:
  - What do you tell the family regarding risks and benefits?
    - Risks for established adverse events (eg, SCFE, pseudotumor, type 2 DM)?
      - Probably similar to idiopathic GHD
    - Risk of recurrence of medulloblastoma?
      - Same as survivors not treated with GH
    - Risk of second neoplasm?
      - Possible small increased risk of secondary non-CNS neoplasms compared to survivors not treated with GH
    - Expected growth response to GH?
      - Suboptimal due to prior spinal radiation
    - When is it safe to start GH therapy?
      - >/= 1 Yr disease-free, off all cancer therapy
    - What dose of GH would you use?
      - 0.3 mg/kg/wk

Case 2: Male S/P Chemotherapy for Optic Pathway Glioma

- Age at diagnosis: 5 9/12 yrs
- Age at completion of therapy: 6 10/12 yrs
- Age at referral: 9 4/12 yrs
- Reason for referral: Routine endocrine follow-up
- Family and Past Medical History: Visual impairment noted ~ age 3 yrs, leading to diagnosis of optic pathway tumor. Endocrine evaluation at diagnosis was negative. No similarly affected family members
- Treatment:
  - vincristine, lomustine (CCNU), thiouquanine, procarbazine
  - Cyclophosphamide equivalent dose* (CED) 14.8 gm/m2
Case 2: Male  S/P Chemotherapy for Optic Pathway Glioma

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Case 2: Male S/P Chemotherapy for Optic Pathway Glioma

- Initial visit age 9 4/12 yrs
  - HPI: Doing well, active, extra-support in school. Father has noted some new pubic hair over past several months. No other concerns
  - PE: WDWN, Height 47th percentile; Weight 78th percentile; BMI 85th percentile
    • Clear skin, no café au lait lesions; Tanner II PH, Tanner II-III genitalia, testicular volume 3/3 cc
    - What is your interpretation of the findings on PE?
Case 2: Male S/P Chemotherapy for Optic Pathway Glioma

- What screening endocrine studies would you order at this visit?
  - Free T₄ 0.9 (0.9-1.8)
  - TSH 2.2 (0.4-4.9)
  - Cortisol 13.7 mcg/dl (378 nmol/L)
  - Testosterone 191 ng/dl (normal prepubertal male <10; adult 240-871)
  - LH 2.4 mU/ml
  - FSH 10.4 mU/ml
  - Bone age 11 yrs (CA 14/12). Predicted adult height ~158 cm (62")

- Given these findings, any additional endocrine testing?
  - GH testing
    - Peak GH 5.3 ng/ml (>10) after Arg & Clonidine
    - IGF-1 +1.24 SD for age

- What are your treatment recommendations?
  - GnRH agonist plus GH

Optic Glioma: Neuroendocrine Morbidity (n=166)

Table 1. Predictors included in the multivariate Cox and linear regression models for overall OGS (progression-free (PFS) and endocrine morbidity score (EMS) and endocrine mortality score (EMS) and endocrine mortality score (EMS). The table shows the adjusted hazard ratios (HR) and confidence intervals (CI) for each predictor.

Hoong-Wei G. et al. JCEM. 2015 ahead of print
Under Appreciated Clinical Points

- Importance of obtaining details of therapeutic exposures
  - Drugs
    - Cumulative doses of key drugs (eg, alkylating agents)
  - Radiation
    - Radiation doses to critical endo structures
- Impact of RT to spine (eg, whole spine, abd, pelvis) on growth
  - dose-, volume-, age-dependent
- Impact of treatment on testicular size
  - not a sensitive/reliable index of sexual maturation
- IGF-1/BF3 poor predictors of GH status post-RT, not recommended as a screening tool

Ovarian Function in Survivors of Medulloblastoma/PNET

![Graph showing FSH levels over years post-diagnosis](image)

$^+$ = ASCR
Alkylating Agent Exposure and Risk of Azoospermia: S/Life

Impact of RT on Spinal Growth

Silber et al, JCO 1990
Meet the Expert Session
8:1 – 8:2

Looking beyond nutritional rickets:
From the foetus to the infant
Wolfgang Hogler (Birmingham, UK)

Friday 2 October 08:00 – 09:00 – Hall 2
Saturday 3 October 15:30 – 16:30 – Hall 3
Looking beyond Nutritional Rickets: From Foetus to Infant

Vrinda Saraff, Wolfgang Högler

Department of Endocrinology & Diabetes, Birmingham Children’s Hospital, Birmingham, United Kingdom

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Prevention of rickets in the light of the refugee crisis

Amidst the emerging refugee crisis in Europe, it is important to reflect on our health care systems and focus on strategies to protect people at risk, especially the ethnic minorities. While early diagnosis of the disease and its treatment is important, primary prevention is paramount. Amongst the thousands currently migrating into the heart of Europe in desperation, are pregnant women, infants and children. They are likely to have migrated from countries with inadequate primary prevention programs and infant vitamin D supplementation. Many have darker skin, wear protective skin clothing covering most of their body due to religious and cultural beliefs and consume traditional diets low in calcium. All these factors pose a high risk for nutritional rickets, osteomalacia and hypocalcaemia. Their migration into Europe, away from sunnier climates, increases their risk of bone disease exponentially.

Translating this to clinical practice, a 2 month-old baby boy of African origin presenting to the local Emergency department with a prolonged hypocalcaemic seizure and a serum calcium of 1.5 mmol/L, is not unusual. While recognising severe vitamin D deficiency as the cause of the hypocalcaemic seizure and providing treatment with vitamin D and calcium is good clinical practice, this is only the beginning. It is important to recognise rachitic changes on X-ray and explore the possibility of associated dilated cardiomyopathy. Equally important is recognising the increased risk of the patient’s siblings to have active rickets, and of the mother along with other older family members to have osteomalacia and skeletal myopathy. The evidence suggests that the dietary calcium intake of such families is often very low for cultural reasons, thus rendering them extremely vulnerable to complications from additional vitamin D deficiency. It is therefore vital to raise awareness among other family members, to the lifelong risk of bone disease they are exposed to, particularly during the spring and winter months (the ‘vitamin D winter’) and the need for lifelong vitamin D supplements, especially if they continue living in Europe. Also essential is to ensure that all pregnant women and infants receive vitamin D supplementation, in addition to their scheduled vaccinations.

The ‘at risk’ groups
Deficiencies of Vitamin D and dietary calcium are prevalent globally. Rickets, osteomalacia and hypocalcaemia are well recognised complications, and hypocalcaemic dilated cardiomyopathy (CMP) can be potentially fatal. Vitamin D deficiency stems from geographic location and culture, neither of which can be changed. What can be changed are health care standards. Therefore, from a public health perspective, prevention of vitamin D deficiency requires strategies to increase the population’s serum 25-hydroxyvitamin D (25OHD) levels worldwide.

**Geography**

The UVB spectrum (290-314nm) of sunlight required for cutaneous vitamin D synthesis is influenced by the solar zenith angle, defined as the angle between local vertical and the position of the sun in the sky. This is lowest at higher latitudes and during winter months, meaning individuals residing north of approx. 34 degrees Northern latitude (i.e all of Europe), or south of approx. 34 degrees Southern latitude, will experience a ‘vitamin D winter’. For example, no cutaneous synthesis of vitamin D occurs in northern European cities like Berlin or London (51 - 52 degrees North) between October and April. As diet is a poor source of vitamin D, the vast majority of Northern (90%) or Central (60%) Europeans have 25OHD levels below 50nmol/L at the end of winter, infants being particularly vulnerable.

**Culture**

Rickets is epidemic in most of Africa, Arabia and India despite their proximity to the equator. The commonest cause of rickets and osteomalacia in these countries is a diet very low in calcium combined with protective traditional clothing and pigmented skin which predispose them to vitamin D deficiency. For these reasons, the female Muslim population is at very high risk of osteomalacia and muscle weakness, and their children are predisposed to rickets and hypocalcaemic complications. The risk for symptomatic vitamin D deficiency increases exponentially in at-risk individuals who live, or migrate away from UVB sunlight exposure into the northern or southern hemispheres farther away from the equator.

**Vitamin D vs Calcitriol**

Unprotected skin exposure to sunshine remains the main source of cutaneous vitamin D3 (cholecalciferol) synthesis from 7-dehydrocholesterol, with only a small proportion derived
from dietary vitamin D2 (ergocalciferol). The liver initially converts vitamin D into 25-hydroxy-vitamin D (25OHD), which is further hydroxylated in the kidneys, placenta and other tissues to the active D-hormone calcitriol (1,25(OH)$_2$D). Laboratories measure the inert 25OHD, which represents the body’s storage metabolite of vitamin D. Mistaking the active hormone calcitriol for the natural vitamin D has led to misinterpretation of blood results and serious medical errors. The main function of calcitriol is to increase calcium and phosphorus absorption from the gut. Calcitriol thus serves as the main supplier of bone minerals that are eventually deposited into newly formed bone osteoid. Bone minerals represent the actual substrate for bone material density, while calcitriol is only their supplier. Low vitamin D and low dietary calcium have virtually the same health consequences, and their combined deficiency is most detrimental to bone. While 25OHD reliably represents the body’s vitamin D status, serum calcium is a poor indicator of calcium status.

**Defining Deficiencies**

Confusion regarding the definition of vitamin D deficiency stems from a tendency to focus solely on 25OHD levels (the ‘supplier’) whilst ignoring calcium intake (the ‘substrate’). The global consensus on rickets states that the vast majority of children with nutritional rickets have 25OHD levels below 34nmol/L, which is in agreement with the Institute of Medicine’s categorisation of vitamin D status as normal if 25OHD is >50nmol/L, insufficient if between 30-50nmol/L, and deficient when levels are <30nmol/L. However, when dietary calcium intake is extremely low (< 300mg/day), rickets can develop in the presence of normal 25OHD levels, as seen in children from African and India. Similarly, ‘vitamin D deficiency rickets’ only develops in children with a low calcium intake (Figure 1). Sufficient dietary calcium can therefore offer some protection from developing ‘symptomatic vitamin D deficiency’. However, neonates who start their life with vitamin D deficiency, in the absence of vitamin D supplements, are not protected from symptomatic deficiency by breast or formula milk.

**Vitamin D deficiency in neonates and infants**

Phases of rapid growth such as in the foetus and infancy require significantly higher bone mineral supply to ensure optimal bone health. Neonatal 25OHD levels are usually 75% of
the maternal levels. Thus, babies born to vitamin D deficient mothers are also deficient and if not commenced on vitamin D supplements in a timely fashion, can develop symptoms including severe and prolonged hypocalcaemia leading over time to seizures, dilated CMP and/or rickets.

**Hypocalcaemic seizures and tetany**

Hypocalcaemia lowers the threshold for axonal depolarisation resulting in nerve hyperexcitability, which leads to seizures and tetanic muscle contractions. Hypocalcaemic seizures due to vitamin D deficiency are frequently reported in neonates and infants. About one third of unsupplemented infants diagnosed with nutritional rickets in infancy reportedly present with hypocalcaemic seizures and tetany. Hypocalcaemia also reduces myocardial and skeletal muscle contractility leading to hypotonia.

A recent national survey in the UK identified 91 children with hypocalcaemic seizures caused by vitamin D deficiency over a 2-year period, 27% were neonates and 87% were under 1 year of age. As expected, 82% of children were of non-white ethnic origin. Of those who had X-rays taken, 77% showed evidence of rickets. Whilst 55% of infants were breastfed, babies on formula milk, which contains some vitamin D, were not protected from developing hypocalcaemic seizures. While transient neonatal hypoparathyroidism, a distinct maturational phenomenon, can worsen hypocalcaemia, it also provides protection against rickets due to the typically high serum phosphate concentrations. Rickets in infants younger than 6 months is associated with higher serum phosphorous levels when compared to older children. Transient neonatal hypoparathyroidism thus partly explains the lack of bone disease in early infancy.

**Hypocalcaemic Dilated Cardiomyopathy (CMP)**

Hypocalcaemic dilated CMP is the most serious complication of vitamin D deficiency resulting in heart failure, arrhythmia, cardiogenic shock and death. Although rickets and CMP often co-exist they are managed by two different subspecialties, and a high degree of suspicion is required to avoid missed diagnoses. Hypocalcaemic CMP usually affects infants between 3 weeks and 10 months. Most, but not all infants in case series had radiological evidence of rickets. Some of these infants presented with hypocalcaemic seizures or in
cardiogenic shock. As expected, all reported infants were dark skinned, exclusively breastfed and vitamin D deficient, with typical biochemical markers associated with rickets. Of the 16 infants from the London cohort, 12 needed i.v. inotropic support, 8 were ventilated, 6 had cardiac arrest and 3 died.\textsuperscript{13} Prolonged QTc interval is another typical cardiac complication of hypocalcaemia.

**Congenital Rickets**
The foetus takes intrauterine priority over the maternal metabolism resulting in vitamin D deficiency being primarily detrimental to the mother (causing osteomalacia), rather than the baby. However, in extreme cases of severe maternal deficiency, neonates are born with congenital rickets, which has been reported in 80 cases over the last 90 years.\textsuperscript{14} Typically, mothers have osteomalacia with severe vitamin D deficiency, low calcium intake, are mostly hypocalcaemic at delivery and had not taken vitamin D supplementation during pregnancy. Congenital rickets can also arise from chronic maternal hypocalcaemia due to other causes.

When rickets presents itself during the 2\textsuperscript{nd} month of life a congenital origin can also be suspected, but similar to dilated CMP, rickets may just have developed after birth if postnatal life was started with a very low vitamin D status. The serum half-life of 25OHD is about 14-20 days, hence even if born to vitamin D replete mothers, a postnatal drop in 25OHD is expected at 8 weeks of age, especially in those not on supplements.

**Pre-Rickets and Nutritional Rickets**
Classical nutritional rickets in infants typically presents between 6-15 months of age. The global consensus recommendations state that the diagnosis of rickets requires radiographic confirmation.\textsuperscript{5} However, the pathology that leads to clinical presentation with bowed legs or widening wrists, as the main symptoms would have started several months before. Clearly it takes time to profoundly disturb the growth plates, wash out minerals from existing bone and create the typical signs of rickets and osteomalacia. Thus, from a bone perspective, there exists a phase of “pre-ricks” where the damage begins. The typical biochemical features of developing rickets can be detected in the blood stream before the radiological signs become apparent, including an elevated alkaline phosphatase activity and parathyroid hormone levels, along with normal or low serum calcium and/or hypophosphataemia.
Management

The global consensus group recommends that rickets, whether infantile or congenital, is treated with vitamin D (cholecalciferol or ergocalciferol) and calcium for a minimum of 3 months, followed by supplementation doses of vitamin D (Table 1). The same treatment regimen applies to symptomatic vitamin D deficiency associated with hypocalcaemic seizures and CMP. In high-risk groups, this supplementation ideally needs to be lifelong, or at least during the vitamin D winter, unless food fortification with vitamin D becomes the national standard.

Treatment of hypocalcaemic seizures and dilated CMP also involves short-term administration of intravenous calcium infusions and oral alfacalcidol (or calcitriol) to rapidly normalise serum calcium. Whilst antiepileptic drugs may be administered temporarily to stop a prolonged seizure, what is required is the correction of serum calcium to prevent further seizures. CMP often requires prolonged intensive care, inotropic support, diuretics, ventilation, and sometimes extracorporeal membrane oxygenation. Dilated CMP caused by hypocalcaemia is reversible however left ventricular ejection fraction can take between 2 to 12 months to normalise. 13

Prevention of rickets - supplementation vs food fortification

Universal vitamin D supplementation for infants

Nutritional rickets, osteomalacia and hypocalcaemic complications are predominantly found in countries with poor primary health care standards, irrespective of geographical location. On the European continent, which is exposed to a vitamin D winter in its entirety, universal supplementation of infants with vitamin D has virtually eradicated rickets. However, implementation of vitamin D supplementation in the UK remains a problem. Strong evidence from randomised trials confirms that 400 units of vitamin D daily prevent rickets in infants. 15 For example, a supplementation program in Turkey reduced the prevalence of rickets from 6% to 0.1%. 5 However, the challenge of protecting the rest of the population, beyond infancy, still remains.

Food fortification
The most practical and cost-effective way to improve the population’s 25OHD level for the prevention of rickets and osteomalacia is by fortifying food with vitamin D. Finland, Canada, and USA are successfully fortifying milk with vitamin D. In the interest of public health, such fortification programmes need to be implemented globally. The global consensus recommendations state that such programmes need to be well designed, include traditional food sources as well as political lobbying for them to succeed.

Responsibility of Health Care Professionals

Neonates and infants have the basic right to be protected from harm. Providing vitamin D supplementation and vaccinations is the responsibility of maternity units, paediatricians and other primary healthcare providers. The Departments of Health in most western countries recommend vitamin D supplementation in the first year of life, as a minimum. For this to be successful, specific groups of professionals need to be accountable, and families provided with a financial incentive to attend routine health checks with their babies. Prevention strategies appear to work well in countries where the first healthcare professional to come in contact with a pregnant woman, or a newborn child, has the responsibility to provide information, start and supply vitamin D supplements. Repeat vitamin D prescriptions and supporting information are provided either by the community paediatrician or family doctor delivering routine care. Identifying individuals at risk and recommending vitamin D supplementation does not require routine measurement of 25OHD, instead some very basic medical knowledge on ethnicity, geography and culture will suffice.

Key Learning points:

- Vitamin D deficiency is a major global public health priority, and rickets and osteomalacia are on the rise worldwide.
- All infants, pregnant women and individuals from high risk groups require supplementation, and food fortification programs should be implemented to ensure nutritional sufficiency of vitamin D and calcium for the whole population.
- Symptomatic vitamin D deficiency and dietary calcium deficiency manifest in different forms, affecting the brain, heart, muscles and bones in newborns and infants.
• While most symptoms resolve on treatment, rickets can have serious complications, including death from cardiomyopathy or obstructed labor, myopathy, seizures, pneumonia, lifelong deformity and disability, impaired growth, and pain.

• Abnormalities can start in the first days of life or even in utero when mothers are deficient and babies are not commenced on vitamin D supplements at birth.

• Vitamin D deficiency is fully preventable by ensuring pregnant and lactating mothers have an intake of at least 600 IU/day, and infants are supplemented with 400 IU/day, of vitamin D.

• The global consensus recommendations for the prevention and management of rickets provide a valuable framework for implementation of prevention strategies and food fortification programs.

• Until fortification programs become universally available, maternity units, paediatricians and in particular family doctors need to identify the families at risk of symptomatic vitamin D deficiency, also recommend and supply supplements, at least during the vitamin D winters.

References:


Figure Legend

Figure 1: Rickets develops when mineral supply to bone decreases, either due to lack of sunshine exposure (cutaneous vitamin D production) or poor calcium intake. This three-stage classification of vitamin D status (represented as the sun) and calcium intake (represented by glass of milk) has been proposed by the global rickets consensus group to explain pathophysiology of rickets.\textsuperscript{5}
<table>
<thead>
<tr>
<th>Osteoid &amp; Growth Plate Mineralization</th>
<th>Vitamin D - Calcium Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal - Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal - Insufficient</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Insufficient - Normal</td>
</tr>
</tbody>
</table>

- Early Biochemical Abnormalities

- Normal
- Deficient - Normal
- Insufficient - Insufficient

- Rickets Osteomalacia

- Insufficient - Deficient
- Deficient - Insufficient
- Deficient - Deficient
Table 1: Treatment of symptomatic vitamin D deficiency for a minimum of 3 months, followed by supplementation doses

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily dose (IU)</th>
<th>Single dose (IU)</th>
<th>Maintenance daily dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For 90 days</td>
<td>oral or i.m.</td>
<td></td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>2000</td>
<td>N/A</td>
<td>400</td>
</tr>
<tr>
<td>3 - 12 months</td>
<td>2000</td>
<td>50,000</td>
<td>400</td>
</tr>
<tr>
<td>12 months – 12 years</td>
<td>3000-6000</td>
<td>150,000</td>
<td>400</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>6000</td>
<td>300,000</td>
<td>400</td>
</tr>
</tbody>
</table>

Ensure a daily calcium intake of at least 500 mg. Reassess treatment response after 3 months as continuation of treatment may be required.