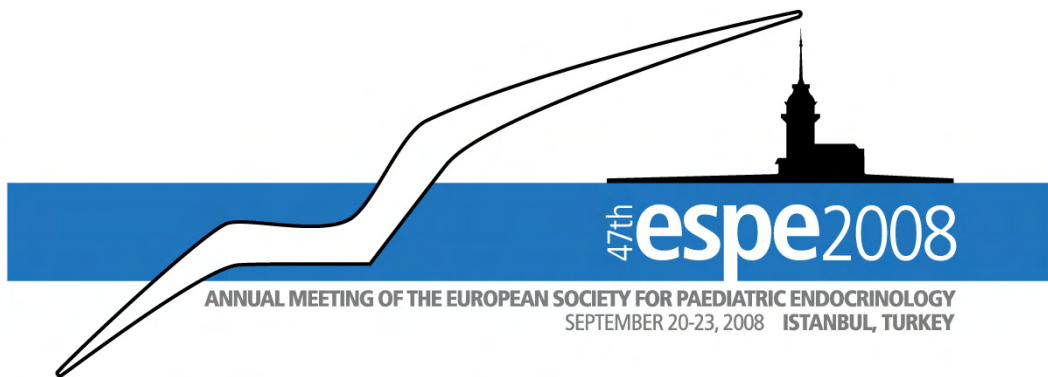


# Meet the Expert Sessions

## HANDOUTS

*These sessions are interactive and located in smaller rooms. Seats are limited and will therefore be allocated on a “first-come-first-served” basis, please be on time.*



## Meet the Expert Session

1:1 - 1:2

### Type2 DM in children

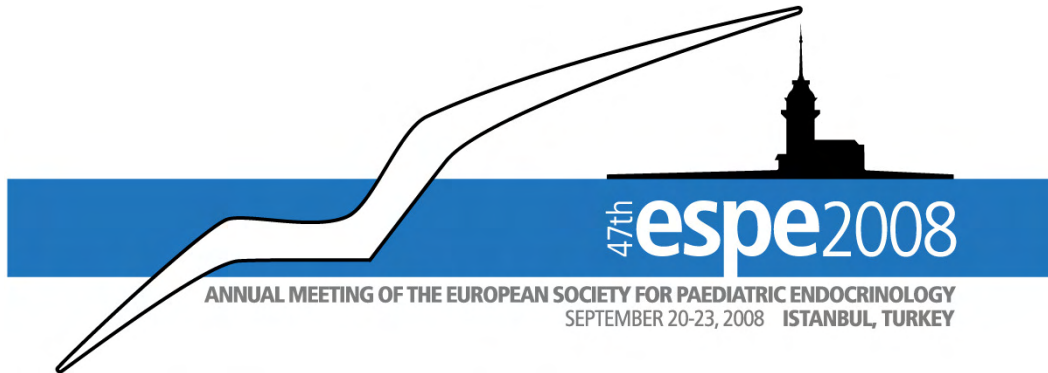
*Neslihan Güngör, Gebze, Turkey*

Sunday September 21

09:15 - 10:15

15:15 - 16:15

Topkapi A



## **Meet the Expert Session**

**2:1 - 2:2**

### **Management of childhood and adolescent obesity**

*Ewa Malecka-Tendera, Katowice, Poland*

Sunday September 21

09:15 - 10:15

15:15 - 16:15

Topkapi B

## Management of childhood and adolescent obesity

Ewa Malecka-Tendera. Dept. Paediatric Endocrinology and Diabetes, Medical University of Silesia, Katowice, Poland

Obesity - a pandemic of 21 century- is affecting more than a billion people worldwide. Two to three times more people are overweight. Unfortunately this growing problem is concerning also children of various ages.

### Epidemiology

Over the past 30 years the prevalence of overweight and obesity in children has been increasing dramatically in most of the developed countries. There has been a trend towards its increasing prevalence in developing countries and in some parts of Africa the problem of childhood overweight has replaced malnutrition<sup>1</sup>. There are strong national differences in prevalence of childhood obesity. Approximately 30% of children in the United States are overweight or obese. In Europe a review of 21 surveys indicated generally lower levels of overweight among children from the countries of central and Eastern part of the continent compared to the countries surrounding the Mediterranean sea<sup>2</sup>.

### Risk factors

This increased incidence of childhood obesity is multifactorial as it cannot be blamed on genetics or environment alone. It is obviously not possible for the gene pool to change in one or two generations. Genes may play a permissive role in fat storing paired with sedentary life style and energy dense diet. Maternal and paternal obesity significantly increase the risk of overweight in their children as well as the maintenance of increased body fat mass into adulthood.<sup>3</sup> Furthermore, parents commonly do not perceive their children as overweight or do not consider obesity as risk factor of impaired physical health<sup>4</sup>. During the past two decades there was a dramatic change in the lifestyle that affected also the young generation. The increasing amount of time, instead of playing outside, children are spending watching television or playing computer games. This habit is related with parents' perception of the neighbourhood as unsafe and reluctance to allow their children to go out to play<sup>5</sup>. Television watching is directly linked to childhood obesity not only due to the inactivity but also due to the energy dense food advertising<sup>6</sup>.

### Comorbidities

Childhood overweight is associated with several adverse consequences. Obese children are at high risk for adult obesity and obesity in adults leads to increased morbidity. However, as the incidence of childhood obesity has increased, paediatricians face the health problems that were restricted formerly to the adult patients.

Type 2 diabetes (T2DM) is now diagnosed in about 20% of pubertal children referred to diabetic clinics in US<sup>7</sup>. In Europe, although less common, it is present in ethnic minorities but also reported in obese Caucasian adolescents, mostly girls with positive family history for T2DM<sup>8</sup>.

Metabolic syndrome (MS) is being identified in up to 30% of obese children. Males of Hispanic origin are at the highest risk, however abdominal obesity increases the risk of MS in all overweight adolescents. Children who have components of MS tend to continue with them into adulthood. There are no definite criteria of the MS for paediatric age group and very limited paediatric reference values for waist circumference in Caucasian children<sup>9</sup>.

Non-alcoholic steatohepatitis (NASH) is an increasing clinical problem in obese children and adolescents<sup>10</sup>. It is a clinical-pathological condition in which liver biopsy shows the signs of steatosis, inflammation and hepatocyte destruction. Its' natural history may have a benign course without severe liver function impairment or in rare cases - progression to cirrhosis. Most children are asymptomatic and a clinical challenge is to identify those at risk for progression to cirrhosis as the candidates for potential therapy.

Obstructive sleep apnoea syndrome (OSA) is strongly associated with obesity. In patients with OSA sleep architecture is disrupted with several obstructive episodes and arousal every night.<sup>11</sup>

## Prevention

In 2003 the American Academy of Paediatrics issued a policy statement on prevention of paediatric obesity and overweight<sup>12</sup>. It states that paediatricians should recognize children at risk for obesity, calculate and plot BMI to identify weight gain and monitor obesity related co-morbidities. Other strategies should be breastfeeding encouragement, healthy eating habits and physical activity promotion as well as limitation of TV viewing.

Prevention of obesity in children should be the first line of treatment. However it is doubtful whether obesity is preventable using currently available intervention strategies. Data from randomized trials to support any particular strategy to prevent the development of overweight in children are lacking.

## Management

Diagnosis of obesity is relatively simple. BMI is the most practical measure and calculated value should be plotted on charts with age and sex reference values. Clinical examination should be focused on ruling out the rare causes of obesity like:

1. Endocrine problems (usually short stature or decreased growth velocity)
  - Hypothyroidism
  - Cushing's syndrome
  - Growth hormone deficiency
2. Chromosomal abnormalities e.g. Prader-Willi syndrome

The assessment of obese child should also include

- BP measurement (with suitably sized cuff and table for norms for age)
- Fasting lipid profile
- Fasting glucose level (or OGTT if family history positive for T2DM)
- Liver function
- Endocrine function\* (if evidence of endocrine disease or short stature)

\*(It is noteworthy that in obese children TSH may be moderately increased with T<sub>3</sub> and T<sub>4</sub> within normal limits. Morning cortisol may also be moderately increased and GH may be low with IGF-1 within normal limits)

Comorbidities such as hypertension, severe dyslipidemia, type 2 diabetes should be managed when identified without waiting until weight loss is achieved.

## Treatment

Not just children or adolescents but the entire family and all caregivers should be involved in the treatment program to promote the environmental changes essential for the long term success<sup>13-15</sup>. Patient and parents have to be informed that the goal of treatment is to promote permanent changes in a life style, not just a short term weight loss Treatment decisions depend on several factors and should be tailored to

- a. Age
- b. Degree of overweight
- c. Comorbidities
- d. Nutritional habits
- e. Level of commitment of child and/or family to change

Some general rules according to the age of the patients are:

### Infancy

Infants at risk for obesity are those of obese parents with rapid weight gain but also children with low birth weight, because rapid catch-up growth is associated with higher rates of obesity and metabolic syndrome. Sustained breast feeding should be encouraged as well as late introduction of solid foods with strong emphasis on vegetables.

### Toddlers

In overweight toddlers diet should be broadened with emphasis on fruit and vegetables and sweetened beverages or juice should be replaced with water. Hours of TV should be minimized with no TV watching during meals. No food or snacks for rewarding, no encouraging eating beyond satiety, no "clean up your plate" rules. Strong parental positive modelling.

### School children

Same as above plus - family based meals should be emphasized, fast-food meals and breakfast skipping avoided. We need to support healthy body image and encourage outdoor play and recreational sports with strong family involvement.

### Adolescents

Family is having less control over eating habits and physical activity. Eating out (particularly at fast-food places) has social value and concerns about weight loss become usually unrealistic. Meal skipping (mostly breakfast) is common. Depressive symptoms, binge eating and decreased self-esteem may need psychological support. Assessment of readiness of the patient to make the lifestyle changes is the first step of treatment. The primary goal of treatment is healthy eating and increased physical activity, not achieving the ideal body weight.

Treatment interventions are based on lifestyle changes: diet modification and increased physical activity. Overall assessment of patients eating habits is performed to identify foods and eating patterns, although obese persons used to underreport their food intake. In children under 8 years of age and older with mild obesity, normocaloric balanced diet is suitable to obtain prolonged weight maintenance. It is based on 4-5 meals with 60-65% low glycemic index carbohydrates, 10-12% proteins and 25% fat. Specific foods like saturated fats, salty snacks and high glycaemic foods should be reduced or eliminated and children must be educated to eat vegetables, fruit, fish and whole grain products, although local nutritional habits must be taken under consideration. Soft sugary drinks should be replaced with water. In older or more obese children diet should be restricted to produce mild negative energy balance. Exercise should be tailored to the child's fitness ability. It is essential to change sedentary behaviour by restricting TV viewing, video games and internet surfing hours.

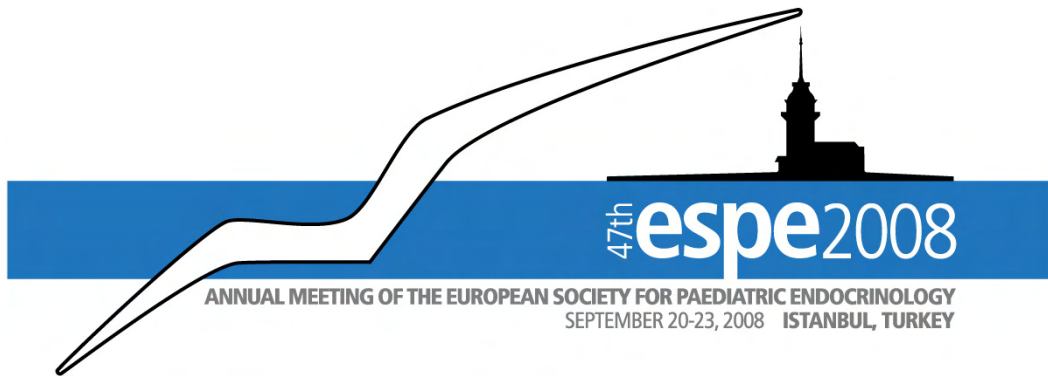
Aggressive approaches to treatment for severely overweight children and adolescents include restrictive hypocaloric diets, drug therapy and bariatric surgery. They should be considered only in morbidly obese patients with severe co-morbidities<sup>14-16</sup>. Very low calorie diets result in rapid weight loss but should not be used in long-term treatment and require physicians monitoring. Currently approved drugs for management of obesity in adolescents (>16 years old) are sibutramine and orlistat. Metformin, insulin sensitizer, is administered to children with T2DM but in some trials it increased weight loss in obese teenagers if added to life style modification<sup>16</sup>.

Bariatric surgery may be indicated in selected subjects with extreme obesity and severe comorbidities<sup>17</sup>. Potential candidates for this type of treatment should be referred to centres with multidisciplinary weight management teams. Patients and their families should be aware of possible risks and side effects of individual bariatric surgical procedures and fully understand that it is an effective weight loss tool only when patients comply with recommended dietary and physical activity regimen.

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## **Meet the Expert Session**

**3:1 - 3:2**

### **Endocrine management of cancer survivors**

*Helene Spoudeas, London, United Kingdom*

Sunday September 21

09:15 - 10:15

15:15 - 16:15

Galata

## Endocrine Late Effects of Childhood Cancer

Meet the expert sessions Istanbul ESPE 2008-09-21

Helen A Spoudeas MBBS DRCOG FRCP FRCPCH MD

London Centre of Paediatric and Adolescent Endocrinology  
Neuroendocrine Division  
Great Ormond Street and University College Hospitals London UK

### AIMS OF SESSION

1. Definitions and Challenges of Topic, Terminology and Service Delivery:
  - a. 'Endocrine' - Broad Topic
    - i. Central vs target gland -
    - ii. 2<sup>o</sup> Consequences - Morbidity and Mortality  
eg diabetes, metabolic syndrome, osteopaenia, tumorigenesis, QoL  
Psychology - hormones important to mood, wellbeing, function  
Late Mortality - life-threatening hormone deficiencies
  - b. 'Late'-
    - i. Diagnostic signs vs evolving- is it truly late?
    - ii. Pre-symptomatic surveillance vs symptomatic (ie late) therapy
    - iii. Very long term? necessity and purpose of continued f/up?
  - c. 'Effects'
    - i. Cause or Consequence
    - ii. Disease or Treatment - Induced - and which therapy?
    - iii. Morbidity vs Mortality
    - iv. Quantity vs Quality of Life - ethical costs & balanced choices-  
whose? medical vs personal - patient empowerment
  - d. 'Childhood' -
    - i. Developing organism- endocrine maturity vital process
    - ii. Timing of insult and duration of effect - cf young adult treated as  
child vs treated as adolescent /young adult
    - iii. Overlapping age- transitions determine symptomatology and service  
development, and specific electronic health record
    - iv. Reproductive Capacity and Care of Pregnancy and Offspring ?  
as yet inadequately or not considered
  - e. 'Cancer' -
    - i. Cancer only vs Life-threatening disease or tumours
    - ii. If treatment includes surgical, radiation and high dose therapies  
used in cancer . (NICE UK)  
Eg include 'benign' brain tumours (eg craniopharyngioma, low grade  
astrocytoma, optic gliomas, pituitary tumours) and bone marrow  
transplants for non oncological condns where radiation or chemo-  
based strategies used
2. (Controversial) Topics restricted to Neuroendocrine and Reproductive
3. Illustrative Cases highlighting patient , family and physician dilemmas and choices-  
in particular
  - a. pubertal progress and fertility,
  - b. adult GH replacement therapy,
  - c. quality vs quantity of life outcomes and its determinates ,
  - d. late morbidity and mortality
  - e. issues of service delivery, transitional care, self-help 'empowerment'
  - f. ethics of 'cost' - benefits

4. Literature Evidence-Based Review
  - a. Neuroendocrine Deficits and Causation
    - i. - Radiation not the only culprit
    - ii. - Evidence for disease & surgical effects (cranios + optics)
    - iii. - Importance of early endocrine treatment for salt and water balance and diabetes
    - iv. - Evidence that substituting chemotherapy may cause
      - ↑ toxicity (all levels of HPA-target gland axis)
      - ↑ morbidity, ↓ patient experience and QoL
      - **No** realistic ↑ in long term 'cure'
  - b. Algorithms for
    - i. Likely Anterior Pituitary Consequences according to Treatment and Tumour position
    - ii. Likely hypothalamic/posterior pituitary disturbances (pubertal progress, salt and water imbalance) according to tumour and treatment, and a management algorithm
    - iii. Likely sub/in fertility risk according to treatment strategies
  - c. Availability, Effectiveness and Ethics of Protective and/or Treatment Strategies
    - i. for GH deficiency
      - for childhood
      - for the adult GH deficiency syndrome
    - ii. for sexuality, sex hormone replacement and reproduction
      - at HPA level
      - at target gland level
      - from assisted reproduction techniques
5. Suggested Strategies
  - a. Introduce e-record model and SUCCESS service
  - b. Recommended baseline minimum data set and patient information
  - c. Transition services - integrated with oncology, neurosurgery, BMT
  - d. Levels of Patient Care. - and Algorithms
    - i. Treatment type and intensity, organ(s) involved and patient age and sexual maturity *and choice* determine
      - f/u need, frequency, duration, specialty services
      - mode of delivery (direct, e- or telecomm, Gp, self-referral)
      - personnel
      - preventative or life-enhancing (vs life sustaining) therapies
6. Future Needs
7. Suggested Literature Review

#### Overview (review)

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### **Neuroendocrine Toxicity**

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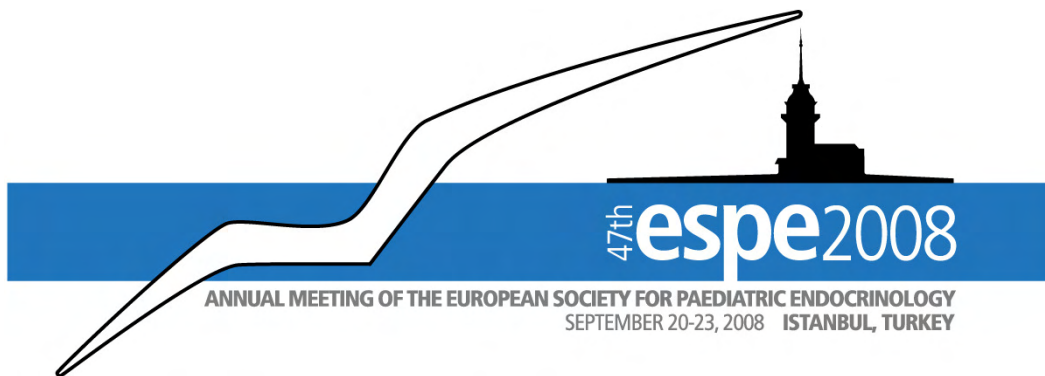
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## **Meet the Expert Session**

**4:1 - 4:2**

### **Hirsutism and menstrual disturbances in adolescents**

*Lourdes Ibañez, Barcelona, Spain*

Sunday September 21

11:00 - 12:00

Monday September 22

11:30 - 12:30

Topkapi A

## Hirsutism and Menstrual Disturbances in Adolescence

Lourdes Ibáñez  
Hospital Sant Joan de Déu  
University of Barcelona  
Spain

**(1) Hirsutism** refers to excessive body hair growth in women, according to a male pattern. Approximately 5% of women of reproductive age are hirsute, as judged by a score of 8 or more on the Ferriman-Gallwey scale, which is the most widely used method to score the extent of hair growth in androgen-sensitive sites. Hirsutism should thus be distinguished from so-called hypertrichosis, which is defined as hair excess according to a generalized pattern and which mostly results either from an inherited trait or from the use of medications such as glucocorticoids, phenytoins, minoxidil or cyclosporine.

**(2) Menstrual irregularities** are common in the first 2 post-menarcheal years; about half of the menstrual cycles in this period are still anovulatory - so-called *physiological adolescent anovulation* (PAA). In some girls, menstrual irregularities persist and are accompanied by high LH and testosterone levels, and are among the first signs of ovarian hyperandrogenism or polycystic ovary syndrome (PCOS). Irregular menses may be a warning sign for eating disorders, and may also be related to strenuous physical activity, for example, in elite athletes.

**(3) The combination of hirsutism and menstrual irregularities** more than 3 yr after menarche is suggestive of an underlying disorder, most frequently, ovarian androgen excess or PCOS.

### **(4) PCOS**

#### **1. Definition of PCOS**

Since 1935, the definition of PCOS is a matter of debate; 3 definitions are in use.

- I. The first originated in a conference sponsored by the U.S. National Institutes of Health (NIH) in 1990. The conclusion was that the criteria for PCOS should include:
  - 1) hyperandrogenism and/or hyperandrogenemia, and
  - 2) oligo-ovulation (with exclusion of other known disorders).
- II. According to a conference held in Rotterdam in 2003, and sponsored by the European Society for Human Reproduction and Embryology, and by the American Society for Reproductive Medicine, the diagnosis of PCOS requires at least 2 of these 3 features:
  - 1) clinical and/or biochemical hyperandrogenism,
  - 2) oligo- and/or anovulation,

3) polycystic ovaries on ultrasound.

Again, other known disorders had to be excluded.

III. In 2006, the Androgen Excess Society returned to two criteria:

- 1) Clinical and/or biochemical hyperandrogenism;
- 2) Ovulatory dysfunction and/or polycystic ovaries on ultrasound.

In adolescent girls, we suggest to stick to the original NIH criteria.

## **2. Pathophysiology of PCOS**

PCOS is regarded as a polygenic disorder with influences from the environment and the lifestyle modulating the genetic trait, and explaining the heterogeneity of the phenotype.

The mainstay of PCOS genetics has been the candidate gene approach; however, candidate gene selection has been limited by the scarce knowledge on PCOS pathogenesis. Candidate genes studied - to date >100 - have generally targeted loci regulating four areas: a) steroid biosynthesis and action; b) gonadotropin synthesis and action; c) weight and energy regulation; d) insulin secretion and action. Most recently, candidate genes associated to inflammation or hypercoagulability have also been assessed; however, none of them has been universally agreed upon.

A recent hypothesis proposes that PCOS has developmental origins, the genetic predisposition to secrete excess insulin and/or androgens being activated in early life and/or in puberty, and resulting in variable degrees of hyperinsulinemia, hyperandrogenemia, and excess LH. These abnormalities may be further enhanced by diet and lifestyle, and evolve towards the full clinical spectrum of PCOS.

## **3. Major Subgroups at PCOS risk**

Identifying girls at risk for PCOS offers the potential of preventing or delaying the long-term complications associated with the syndrome.

Obesity associated to insulin resistance in early childhood seems to be a PCOS risk factor. Prenatal growth restraint followed by excessive catch-up growth in weight may lead to precocious pubarche and/or early puberty-menarche, followed by hyperinsulinemic androgen excess. PAA may also end up in full-spectrum PCOS. Finally, congenital adrenal hyperplasia (CAH) and other virilizing disorders may subsequently associate to PCOS.

## **4. Clinical Presentation of PCOS**

*The combination* of slowly progressive, moderate-to-severe hirsutism, menstrual irregularities, acne, acanthosis nigricans, obesity and/or central fat excess suggests the presence of hyperinsulinemic androgen excess, and thus PCOS.

*The medical history* should address the presence of familial traits of PCOS, as well as the existence of risk factors in the patient, such as underweight at birth, overweight in childhood, early pubarche, early puberty and early menarche.

The personal history should screen for the use of medication (valproic acid; antipsychotic drugs) and ascertain the age at onset of hirsutism, as well as the pace of its progression.

**The physical exam** should include height and weight, to derive body mass index. The degree of hirsutism can be scored by Ferriman & Gallwey scale; a score of 15 or more suggests underlying hyperandrogenism. A score >30 together with clear signs of virilization such as clitoromegaly, balding and increased muscularity is suggestive of an androgen-secreting neoplasm (or of exogenous androgen abuse). A high waist-to hip ratio ( $\geq 0.8$ ) is a surrogate of central fat excess. The presence of acanthosis nigricans - pigmented skin areas usually in the neck or axillae - is associated to insulin resistance.

### 5. Diagnosis of PCOS, and Differential Diagnosis

**The initial diagnostic work-up** should include the Free Androgen Index - equivalent to circulating free testosterone [FAI, total testosterone (nmol/L) X 100 / sex hormone-binding globulin (SHBG, nmol/L)] -- and serum 17-hydroxy-progesterone (17-OHP) in the morning, and either in the follicular phase (cycle day 4-8) or after 2 months of amenorrhea. A normal FAI level ( $\leq 5$ ) is suggestive of so-called *idiopathic hirsutism*. Extremely elevated total testosterone (>200 ng/dL) or FAI levels (>30) together with rapidly developing hirsutism and virilizing symptoms are suggestive of an *androgen-producing tumor*, and measurement of other ovarian and/or adrenal androgens (androstenedione, dehydroepiandrosterone-sulfate) is recommended. The finding of a moderate-to-high FAI (>5-30) is mostly associated to *PCOS*; in these adolescents, fasting glucose and insulin, as well as the lipid profile should also be assessed.

An **ACTH test** is indicated when baseline 17-OHP is >200 ng/dL. ACTH-stimulated 17-OHP responses >1500 ng/dL are suggestive of late-onset CAH due to 21-hydroxylase deficiency; definitive diagnosis requires molecular confirmation. The prevalence of this enzymatic defect among adolescents with clinical hyperandrogenism is no more than ~3%.

An **oral Glucose Tolerance Test** (oGTT) is recommended in girls at risk for glucose intolerance; i.e., those who are obese and those who evolved through the sequence of prenatal underweight and subsequent overweight.

An **ovarian ultrasound** to document the presence or absence of polycystic ovaries is not required for the diagnosis of PCOS by NIH criteria. Moreover, any ovarian imaging should be interpreted with caution as ovarian morphology appears to be co-determined by prenatal growth and as ~10% of asymptomatic adolescents may have polycystic ovaries.

The assessment of **body composition** is of interest for research purposes, and may be helpful in judgments of therapeutic efficacy. In girls with PCOS, the body fractions of fat and abdominal fat are high, even in the absence of obesity, and lean mass tends to be low.

Imaging studies as **abdominal CT or MRI** are mainly needed to visualize a tumor.

## 6. Treatment of PCOS

In overweight and obese girls, advice about *diet and exercise* is important both for improvement of the menstrual symptoms and for prevention of long-term complications, such as type 2 diabetes.

*Cosmetic measures* including hair removal are the cornerstone of care for idiopathic hirsutism, and may be a useful adjuvans for PCOS patients with moderate-to-severe hirsutism, because the reduction of hirsutism with pharmacological intervention may take as long as 9-12 mo .

The aims of *pharmacologic intervention* are not only the improvement of symptoms of androgen excess, but also the correction of the underpinning abnormalities. The treatment should also take into account whether there is a need for contraception.

1. Oral contraceptives (OC's) have traditionally been the first-line therapy for adolescent PCOS, regardless of contraceptive concerns, as they improve hirsutism, acne and cycle irregularities. OC's reduce free testosterone levels, mainly by silencing the ovaries and by raising SHBG levels. OC's with non-androgenic progestins, such as those containing drospirenone (Yasmin®, ethinylestradiol 30 µg + drospirenone 3 mg; Yasminelle®, ethinylestradiol 20 µg + drospirenone 3 mg), and those containing a combination of ethinylestradiol and an antiandrogen (Diane®, ethinylestradiol 35 µg + cyproterone acetate) are among the most prescribed. Recent studies, however, have shown that such combinations, when given in monotherapy, may aggravate insulin resistance, worsen body adiposity, and increase long-term cardiovascular risk.
2. Combined androgen-receptor blockade (flutamide 62.5 mg/d) and insulin-sensitization (metformin 850 mg/d) appears to be safe and effective, not only to counter the immediate symptoms, but also to improve the underpinning endocrine-metabolic state, including ovulation rate, without changing body weight. In case of pregnancy risk, we recommend to add an OC for safety - rather than for efficacy - reasons. Evidence on the long-term use of low-dose flutamide (~1 mg/kg/day) continues to be reassuring for anti-androgenic efficacy as well as for hepatic safety.
3. There is pioneering evidence indicating that low-dose pioglitazone (7.5 mg/d) is capable of further enhancing the benefits of combined flutamide-metformin. However, the safety and efficacy of this combination remains to be confirmed over the longer term.

### (5) Summary and Recommendations

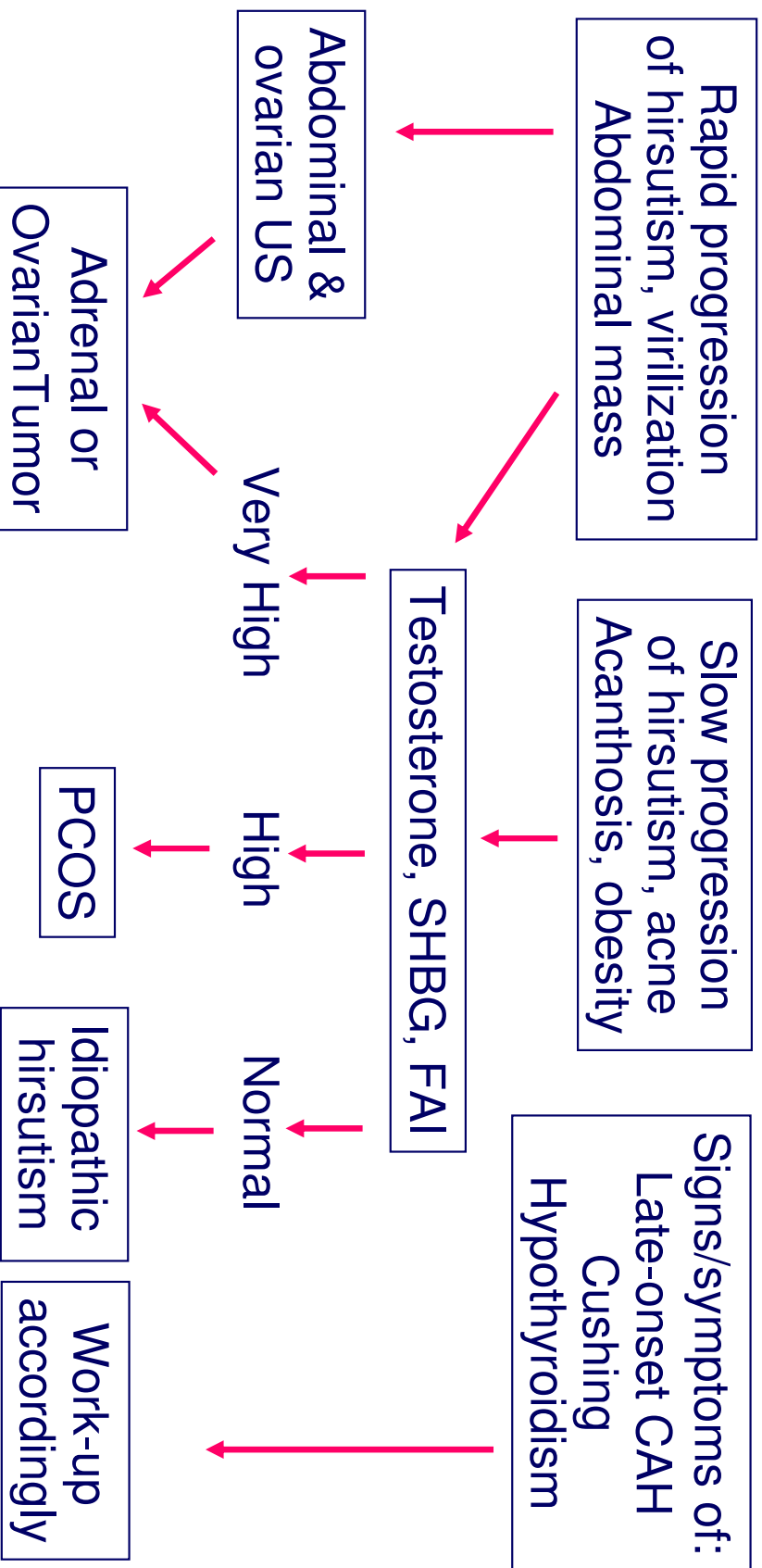
- PCOS should primarily be viewed as a disorder of androgen excess.
- Hirsutism plus menstrual irregularities >3 yr beyond menarche: suggestive of PCOS.
- Major risk factors for PCOS are obesity and the sequence of prenatal underweight and subsequent overweight. Precocious pubarche may be a marker of incipient PCOS.

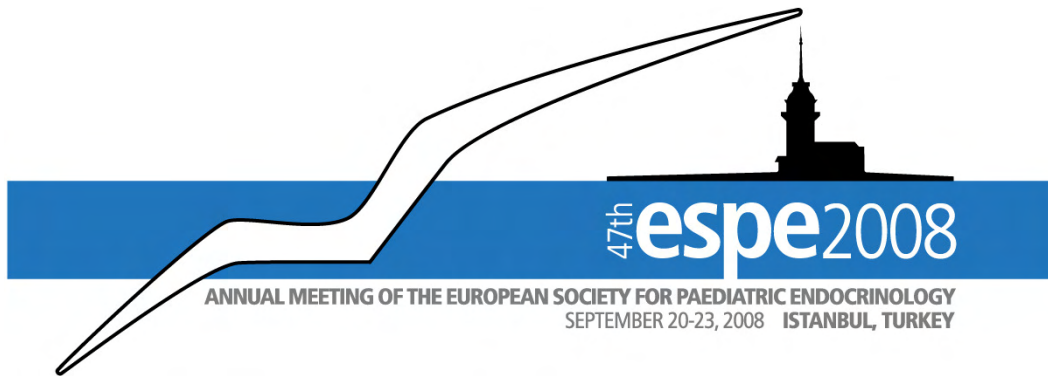
- The medical history and physical exam should address the presence of familial traits of PCOS, the existence of risk factors in the patient, the severity and the progression of hirsutism and/or virilization.
- The initial diagnostic work-up includes Free Androgen Index, serum 17-OHP, and fasting glucose, insulin and lipid profile. Ovarian ultrasound is not required for PCOS diagnosis.
- Therapy includes lifestyle measures in overweight adolescents, and cosmetic measures for hirsutism. Low-dose flutamide-metformin is so far the most effective combination for PCOS therapy in adolescents; in case of pregnancy risk, a non-androgenic OC should be added for safety reasons. The evidence on hepatic integrity during low-dose flutamide treatment continues to be reassuring.

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# Hirsutism & Menstrual Irregularities Differential Diagnosis & Initial Evaluation





## Meet the Expert Session

5:1 - 5:2

### Prader Willi syndrome: difficulties in clinical management

*Maithe Tauber, Toulouse, France*

Sunday September 21

11:00 - 12:00

Monday September 22

11:30 - 12:30

Topkapi B

## Management of children and adolescents with Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder that arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13. The syndrome has characteristic phenotypes including severe neonatal hypotonia, early onset of severe obesity, short stature, hypogonadism, learning disabilities, behavioural problems and psychiatric phenotypes with severe consequences and difficult management issues for patients, families and carers. The lower limit of birth incidence is around 1 in 20,000 to 1 in 30,000 and population prevalence is about 1 in 50,000. Recent epidemiological studies surveys have highlighted the high rates of morbidity and mortality throughout life. PWS is a model showing that early diagnosis and comprehensive multidisciplinary approach including GH treatment prevent complications, optimise quality of life, and prolong life-expectancy. At this time we can assume that in these circumstances, we had completely modified the clinical presentation of most of the children with PWS. The same improvements are needed for adolescents and adult patients and require the experience of the paediatric endocrinologists.

**Early diagnosis:** Evolving phenotype from birth to adulthood means that the clinical features that should lead to a suspicion of the diagnosis depend on the age of the patient (1). The diagnosis of PWS should be evocated in all infants with severe and unexplained hypotonia (2). DNA methylation analysis is the only technique which can both confirm and reject the diagnosis of PWS and therefore should typically be the initial investigation of choice.

### **Management of children and adolescents presenting with PWS**

Early diagnosis offers the opportunity for education of parents (ie *parental guidance*), caregivers and other healthcare professionals to receive and give social, psychological and educational support. In addition, support from patient and family associations is increasingly available around the world. The strong efficacy of Growth Hormone (GH) treatment in these children explained the fact that paediatric endocrinologists are often in the first place to coordinate the care of these infants, children and adolescents. In adult patients the endocrinologists are also in the first row due to the complications of morbid obesity. At any age psychiatrists and psychologists are also needed. We like to say that the care of these patients is based on the core trio constituted by the paediatric endocrinologist, the endocrinologist and the psychiatrist.

**Infants:** Over the last ten years, the majority of cases are now diagnosed during the first months of life. There is no consensus to date on the *optimal feeding regimen*, whether the use of tube feeding is mandatory or should be used only after intensive and persistent nursing has failed, given the theoretical possibility that it could worsen speech problems. *Cryptorchidism* is present in over 80% of boys from birth and *orchidopexy* should be performed ideally during the first or the second year. Children with PWS have muscular hypotonia, decreased muscle mass, psychomotor delay, and reduced motor activity. Training programs, initiated early after birth supervised by *physiotherapists* and maintained by parents, have been used for many years without any evidence base (e.g. earlier onset of walking) but would seem sensible particularly in combination with GH treatment. Although hypotonia improves with age it does persist into adulthood together with reduced muscle mass and so exercise should be a regular part of daily life. *Speech and language therapy* are also important to start very early in infancy combined with parental guidance to help with the impaired articulation and delay in development milestones seen in language acquisition.

### **Management of hyperphagia, obesity and its complications:**

**Natural history:** PWS has been classically described as having two phases: poor feeding and frequently failure to thrive (birth to early infancy) and onset of hyperphagia leading to obesity usually starting between 2 and 4 years. Recent examination of the natural history suggests a more complex progression leading to four main nutritional phases emphasizing the fact that weight increase precedes increase in calorie intake. *Neuroanatomical* abnormalities have been found in the post-mortem hypothalamus from patients with PWS that may underlie the hyperphagia, particularly low oxytocin cell number (4). In addition, fasting and post-prandial plasma levels of the orexigenic stomach-derived hormone ghrelin are greatly elevated in PWS throughout life (5), though do fall after food intake.

Although somatostatin acutely suppresses plasma ghrelin concentrations in PWS patients, appetite is not reduced in children or adults. *Body composition* studies show both increased body fat and reduced muscle in PWS from infancy to adulthood. There is also a reduced *resting metabolic rate* relative to body size, related to the abnormal body composition, which further contributes to a reduction in 24 hour energy expenditure. *Type 2 diabetes mellitus* has been reported in around 25% of adults with PWS with a mean age of onset around 20 years but very few cases had been reported in children.

**Obesity management** : it involves environmental control with early institution of a low-calorie, well-balanced diet, with *regular exercise*, rigorous supervision, restriction of access to food and money, appropriate psychological and behavioural counselling of the patient and family. Early discussion with parents about the inevitability of hyperphagia, even during infancy, is essential for attempts to prevent obesity through their ability to set limits and the strict control of the food. Pharmacological treatment, including available anorexigenic agents, has not been of benefit in treating hyperphagia. Until now restrictive bariatric surgery, such as gastric banding or bypass, have not been shown to reduce hyperphagia or achieve long-term weight reduction and are associated with unacceptable morbidity and mortality.

**Growth and GH status:** around 20% of neonates with PWS have a birth weight below -2SDS while median birth length is most frequently in the normal range. After birth, short stature is almost always present especially during the second year, because of GH insufficiency exacerbated by the lack of a pubertal growth spurt. Mean spontaneous adult height has been reported as around 160 cm in boys and 150 cm in girls. The serum levels of IGF-I are reduced in the majority of children and many adults even in obese patients. Spontaneous growth hormone secretion is reduced and GH peak during pharmacological stimulation test is less than 10 mcg/L in 80% of children. GH testing is not required before GH treatment but we advise to do one if possible.

**GH treatment in children:** the aims of GH treatment in children with PWS are to improve growth during childhood, adult height and body composition. In the USA, GH treatment is labelled for short stature while in Europe, growth retardation is not required in children with PWS for initiation of GH treatment. Using the currently recommended dose of 0.035mcg/kg/d, there is a significant increase in height, growth velocity and a decrease in percent body fat. Lean body mass increased significantly and this effect seems to be sustained. Only a few studies have reported data on adult height and most of them (44 patients) reached normal adult height, 60 % in the KIGS study and 100% in a recent study. Prior improvements in strength and agility that occurred during the initial 2 years were sustained. These improvements during GH treatment might contribute to the higher quality of life and improved socialisation with reduced depression. There is increasing evidence of additional benefit in starting therapy between 6 and 12 months of age particularly in terms of motor development, muscle, head circumference and possibly cognition (6).

#### **Safety and GH treatment**

**Sudden death** : since October 2002, several reports of unexpected death in children with PWS have been published. A recent review including 64 children (28 on GH treatment) suggested a high risk period of death during the 9 first months of treatment (7). Nevertheless the role of GH in these deaths had not been proved. We advised that GH treatment should be started at a low dose, such as 0.009 to 0.012 mcg/kg/day, increasing during the first weeks and months to reach a standard replacement GH dosage of around 1.0 mg/m<sup>2</sup>/d or 0.035 mg/kg/day, monitoring clinical effect and avoiding high IGF-I levels particularly if there is a clinical suspicion of over-treatment (oedema, worsening or new development of snoring, headache, acromegalic clinical features). We think that these patients are highly fragile and that multidisciplinary care is mandatory to optimise the effect of GH.

**Sleep-related breathing disorders (SRBD):** a variety of SRBD has been reported in PWS. Recently, it has been demonstrated that non-obese pre-pubertal PWS children have mainly central sleep apnoea and only rarely OSAS during the night. The number of central apnoea/hypopnoea (AHI apnea/hypopnea index) was increased (mean number of 5/hour) and did not correlate with body mass index. Central sleep apnoea indicates a primary disturbance of the central respiratory control mechanism. When children with PWS are overweight, however, half of them have signs of OSAS.

Five prospective studies have evaluated the effects of treatment with GH on breathing disorders in PWS. Most of the studies are in favour or either no effect of GH or a slight decrease in AHI. In light of these findings we suggest to perform a polysomnography prior GH treatment and to control it soon after the start of treatment (2 to 3 months). In case of difficult access, nocturnal oxymetry could be a minimum. Nevertheless in case of severe obesity or respiratory problems or snoring, the PSG is mandatory. Prior to PSG, ENT assessment with tonsillectomy or adenoidectomy if indicated should be performed. We advise to do this surgery in a children hospital with cardiac and respiratory monitoring. We think GH treatment should not be contra-indicated in children having an abnormal PSG without severe obesity, snoring, and with a normal ENT examination.

**Scoliosis :** Scoliosis is a frequent feature observed in about 40 % of children with PWS with or without GH treatment(8). Unlike idiopathic scoliosis, young children are also often affected, with no gender effect. We observed in our cohort a mean age at start of 7 yrs. Scoliosis is frequently associated with kyphosis particularly in obesity and appears to be bad a prognostic factor. The effect of BMI is not clear. Due to the high frequency of scoliosis even in infants, regular clinical assessment is required at each visit, whether or not they are receiving GH. In addition spinal X-ray and, if appropriate orthopaedic assessment, is advised prior to GH treatment at any age.. Reports of scoliosis worsening during GH treatment may simply reflect its natural history rather than a side effect of treatment in most cases. Cessation of GH is not justified in this situation. Indications for bracing or surgery are the same as in idiopathic scoliosis. Surgical treatment is indicated in severe early-onset scoliosis-kyphosis and in adolescents near skeletal maturity. Complications are more frequent and severe than in idiopathic scoliosis. Such surgery requires a multidisciplinary team with expertise in the management of scoliosis associated with neuromuscular disease and PWS.

**Induction of puberty:** Hypogonadism is a consistent feature in both males and females with PWS and implicates both central and peripheral origins at least in males. Most individuals will have no or delayed and incomplete puberty. Isolated premature pubarche and precocious puberty are not rare and there is no consensus as to management of either of these conditions. We used hydrocortisone in premature pubarche to decrease adrenal androgens when there is associated advancement of bone age. And we recommend to avoid the use of GnRH analogs in children with PWS and early or precocious puberty. At some stage almost all subjects will require hormonal treatment for induction, promotion or maintenance of puberty. Mental retardation should not be a contraindication to allow normal pubertal development nor preclude sex hormone replacement at any age. This will be dictated by local availability and experience of different sex steroid preparations and some investigators have also supported the use of hCG (human chorionic gonadotropin) in boys. The use of transdermal and non-synthetic oestrogen preparations which are usually well tolerated despite skin-picking. It remains to be seen whether concerns about aggressive behaviour during testosterone replacement are justified and could be better controlled with transdermal testosterone.

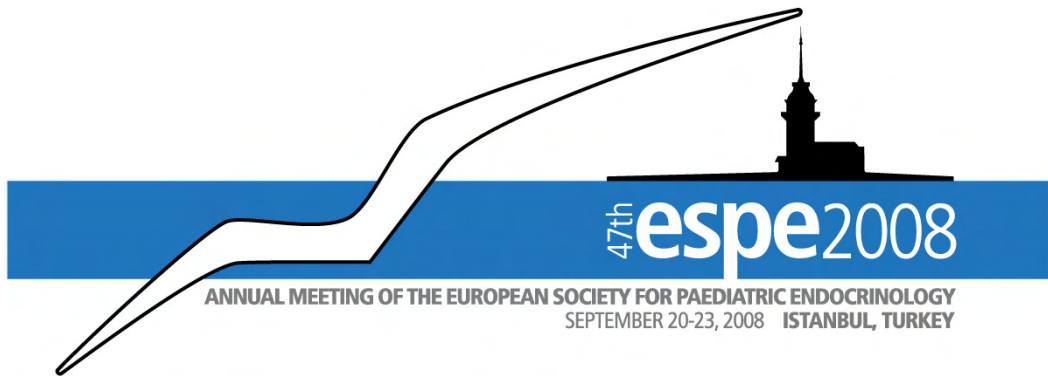
**Hypothyroidism:** it has been reported in a low number of studies and is in our experience often under-evaluated or estimated in children with PWS. The prevalence varies from 6 to 30 % in children with PWS. A recent paper showed the occurrence of hypothyroidism on GH. It may be of central or peripheral origin requiring screening with TSH, free T4 and free T3 measurements prior to and on GH treatment. Replacement therapy is recommended if measurements dictate.

**Transition into adult life:** continuing the benefits of early diagnosis and management into adulthood will require extension of comprehensive care to now involve adult endocrinologists in conjunction with paediatric colleagues, psychiatrists and medical doctors specialized in persons with intellectual disabilities. Health professionals, carers, patients and their families should be encouraged that the earlier diagnosis, multidisciplinary care and use of GH had significant benefit in reducing. Morbidity and altering the disease profile at adolescence. It is hoped that in the future, the prevalence of morbid and life threatening obesity at adolescence will continue to decrease from that seen in historical cohorts. National circumstances often dictate cessation of GH treatment and re-evaluation of GH status at final height. Personal experience is that body composition can rapidly worsen upon stopping GH at that time emphasizing the need for formal GH cessation studies.

This chapter did not develop the psychological and psychiatric aspects. A review with 175 references is in press : **Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M** 2008 Recommendations for the diagnosis and management of Prader-Willi syndrome *J Clin Endocrinol Metab* in press

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3. **Goldstone AP** 2004 Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. *Trends Endocrinol Metab* 15:12-20
4. Fegeirlova
5. **Burman P, Ritzen EM, Lindgren AC** 2001 Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev* 22:787-799
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7. **Tauber M, Diene G, Molinas C, Hébert M** 2008 A Review of 64 Cases of Death in Children with Prader-Willi Syndrome (PWS). *Am J Med Genet A* 46:881-887
8. **Odent T, Accadbled F, Koureas G, Diene G, Molinas C, Pinto G, Tauber M, Cournot M, Sales de Gauzy J, Glorion C** 2008 Scoliosis in patients with Prader-Willi Syndrome. *Pediatrics* In press



## **Meet the Expert Session**

**6:1 - 6:2**

### **Evaluation and management of delayed puberty**

*Jesús Argente, Madrid, Spain*

Sunday September 21

11:00 - 12:00

Monday September 22

11:30 - 12:30

Galata

**Prof. Jesús Argente**

University Hospital Niño Jesús & Universidad Autónoma de Madrid. Madrid, Spain.

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Puberty is defined as the transition between infancy and adulthood when important physical, functional, psychological and psychosocial changes take place. During this period, development of secondary sex characteristics occurs, acquisition of reproductive capacity (the production of mature gametes) takes place and final height is reached after a period of accelerated growth referred to as the pubertal growth spurt. Puberty begins with an increase in pulsatile secretion of the hypothalamic hormone gonadotropin-releasing hormone (GnRH, also called LHRH). However, in spite of the many advances made in the last two decades in our understanding of the neurobiological mechanisms and hormones involved in the regulation of puberty, the primary signal that originates the increase in pulsatile GnRH secretion, and hence the onset of puberty, remains unknown.

**Delayed puberty** can be defined as the *lack of pubertal development at an age of 2 SD above the mean, which corresponds to an age of approximately 14 years for males and 13 years for females, taking both sex and ethnic origin into consideration*. Furthermore, pathological abnormalities, normally partial or transitory hypogonadism, may be present when pubertal changes have started, but puberty does not progress properly and more than 5 years elapse between the first pubertal sign and complete gonadal development in males or menarche in females (detained puberty).

There are multiple causes of delayed puberty. Although it is a frequent occurrence, theoretically affecting around 3% of the population, studies analysing the different aetiologies of delayed puberty are few and lack methodological homogeneity. However, in all studies it is reported that delayed puberty is more frequent in boys and that in both sexes the most frequent variety is ***simple delay in the onset of puberty***. Furthermore, this delay is usually of familiar or idiopathic origin and is known as ***constitutional delay of growth and puberty (CDGP)***. It represents approximately 60% of cases in males and 30% in females. However, many other causes, be they transitory, such as ***functional hypogonadotropic hypogonadism secondary to chronic pathology or stress, or permanent (hypo- or hypergonadotropic hypogonadism)***, could be implicated, indicating the need for adequate diagnostic evaluation of these patients. The differential diagnosis between CDGP and isolated hypogonadotropic hypogonadism unassociated with other alterations is extremely difficult. In many cases, only time and the spontaneous evolution of puberty allow a definite exclusion of hypogonadism.

Pubertal delay is associated with psychosocial disturbances, sometimes severe, that are secondary to the slow growth and/or lack of appearance of the secondary sex characteristics, as well as modifications in body proportion and a possible reduction in final bone density. The start and type of treatment should be individualized depending on the aetiopathogenesis and the clinical and psychosocial repercussions.

## ● Constitutional Delay of Growth and Puberty

The clinical picture of CDGP is characterized by short stature, in comparison with familial height, resulting from a decrease in growth velocity between 2 and 4 years of age, as well as during the peripubertal period (prepubertal deceleration of growth velocity). This short stature is associated with a delay in pubertal development and bone maturation of usually about 2 years.

As mentioned above, CDGP is the most frequent cause of delayed puberty, especially in boys. It can present in a sporadic manner, but it usually has a family component of late maturation. The mode of inheritance and the degree of genetic influence remain unknown; however, recent studies suggest that, although multiple genes may be implicated in CDGP, some genes may have a greater influence and their penetration is modulated by environmental or genetic factors.

Because of the frequency, familial association and the benign clinical picture, and the fact that the majority of patients reach an adult height consistent with that of their parents, most authors consider CDGP as one extreme of the normal spectrum of pubertal development; however, in recent years the apparent benignity of CDGP has been questioned. The known negative psychosocial repercussions of delayed maturation and slow growth, including depression, confrontational behaviour, low self-esteem, poor school performance, reduced peer contact, aggression towards peers, among others, are frequent, especially in the most severe cases. In addition, not all patients reach a height appropriate for their family context. The acquisition of bone mass can be reduced in adulthood, promoting the possibility of future fractures.

The most common treatment in boys is testosterone in the form of depots of testosterone esters with a long half-life (enanthate or cipionate), associated or not with other esters with a short half-life (testosterone propionate), in a single monthly intramuscular injection of 50-100 mg. This form of administration has the advantages of being effective, practical, inexpensive and well accepted by patients.

The incidence of CDGP is much less in girls. As with boys, there is no international consensus on therapy. However, it is recommended that in girls with CDGP, treatment should not be started before a chronological age of 13 years or a bone age of 11-12 years. A very low dose of oestrogen should be used with the aim of not excessively accelerating bone age and thus compromising final height. The most frequent preparation used is oral ethinyloestradiol at a dose of 0.05-0.1 µg/kg per day (2.5-5.0 µg/day). Alternatives to oral ethinyloestradiol are conjugated equine oestrogens and 17β-oestradiol. Conjugated equine oestrogens are administered at a dose of 0.3 mg on alternate days and, after 6 months, if necessary, at 0.3 mg/day. The usual dose of 17β-oestradiol is 5 µg/kg per day and, after 6 months, if necessary, 10 µg/kg per day.

Other alternative therapies (gonadotropins, growth hormone and aromatase inhibitors) will be discussed.

## ● Chronic Pathology

Virtually any child with a chronic disease could present with delayed puberty (due to recurrent infections, immunodeficiency, gastrointestinal disorders, renal disturbances, respiratory illness, chronic anaemia, endocrine diseases, eating disorders, lack of exercise and a number of miscellaneous abnormalities). Depending upon the chronic illness involved, pubertal delay could be the result of undernutrition, emotional deprivation, excess increase in protein degradation, accumulation of toxic substances, stress, secondary effects of therapy or hormonal deficits. Indeed, a component of malnutrition, more or less severe, tends to be constantly present, probably via an effect on LHRH neurons.

Reliable data are not available to establish the incidence or percentage of patients with delayed puberty associated with chronic illness. This is probably because the pubertal delay is often considered as a normal variant or as a not unexpected consequence of the pathology that, in the context of the disease, is not very relevant. However, its clinical importance is increasing, not only because a larger percentage of patients with chronic disorders survive until the age of puberty, but also because of its possible negative repercussions on final height, total bone mass and other psychological aspects of the child.

The degree to which growth and pubertal development are affected in chronic illness depends upon the type of disease and individual factors, as well as on the age at onset of illness, its duration and severity. In many cases the clinical picture is indistinguishable or similar to that which occurs in CDGP and is due to a transitory functional hypogonadism. In other cases, the chronic illness is accompanied by a total absence of pubertal development, in that there is no pubertal onset or, if so, it does not reach completion (definitive hypo- or hypergonadotropic hypogonadism).

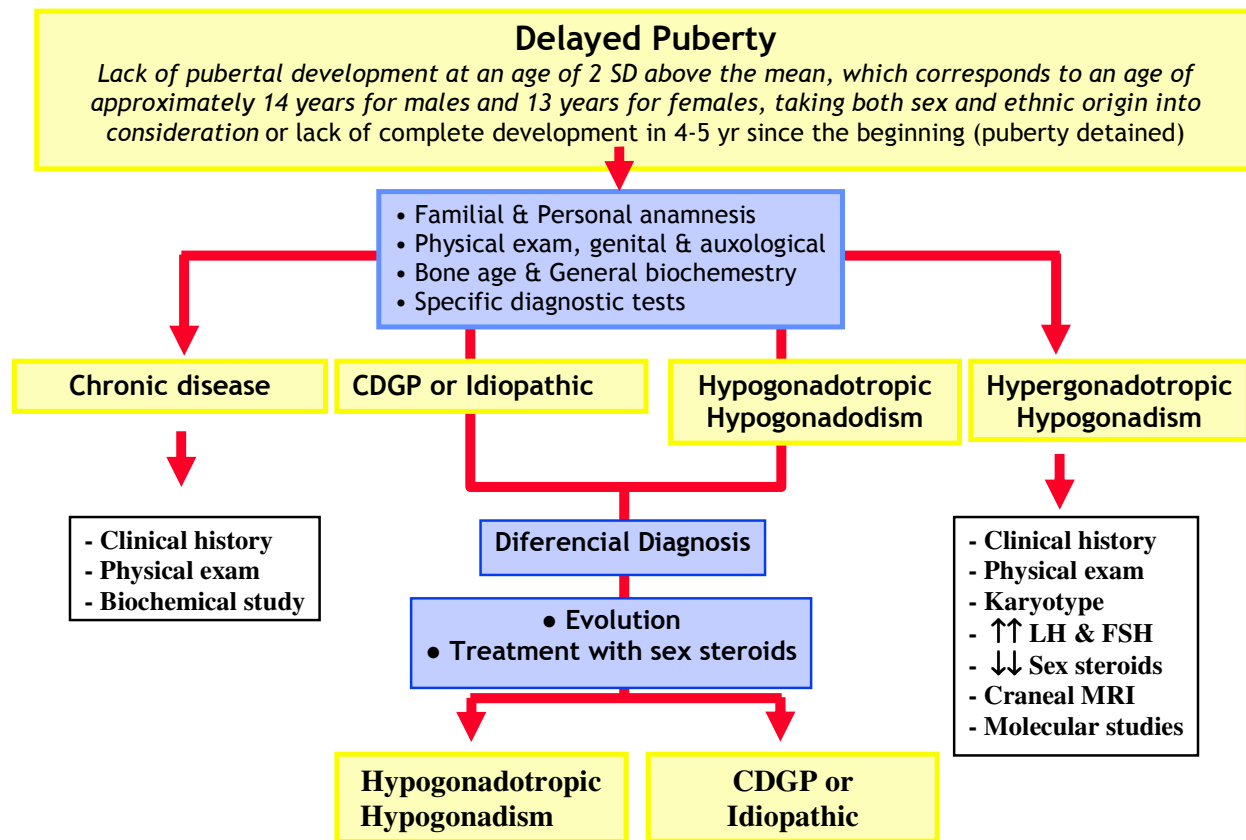
The treatment and prevention of pubertal delay in these patients are based on early and optimal treatment of the underlying illness. Adequate nutrition (sufficient intake of macro- and micronutrients) is fundamental, especially in situations where it is especially compromised. Specific treatment may be necessary in certain illnesses. For example, therapy with desferrioxamine in patients who receive multiple transfusions is necessary in order to minimize iron deposits and the damage produced in the hypothalamus, pituitary and gonads. Obviously, the indication for treatment, as well as the therapy and the most adequate moment to induce puberty, should be individualized for each case. In some cases, as in CDGP, employment of sex steroids may be necessary to induce puberty. In other cases, when definitive hypogonadism is diagnosed or it is necessary to complete pubertal development with detained progression, an adequate protocol of substitution therapy will have to be established.

#### ● Hypogonadism

In hypogonadism resulting from primary gonadal failure (hypergonadotropic) or secondary to hypothalamic-pituitary alterations (hypogonadotropic) congenital or acquired at an early age, puberty does not start or, if it does, cannot be completed. In these situations it is necessary to induce and/or complete the development of secondary sex characteristics. Once pubertal development is completed, a regimen of chronic replacement with sex steroids must be started in order to maintain the secondary sex characteristics, the sexual function and the multiple metabolic functions that depend on the presence of sex steroids. Different gene abnormalities have been recently identified. Therefore, molecular studies must be done when necessary.

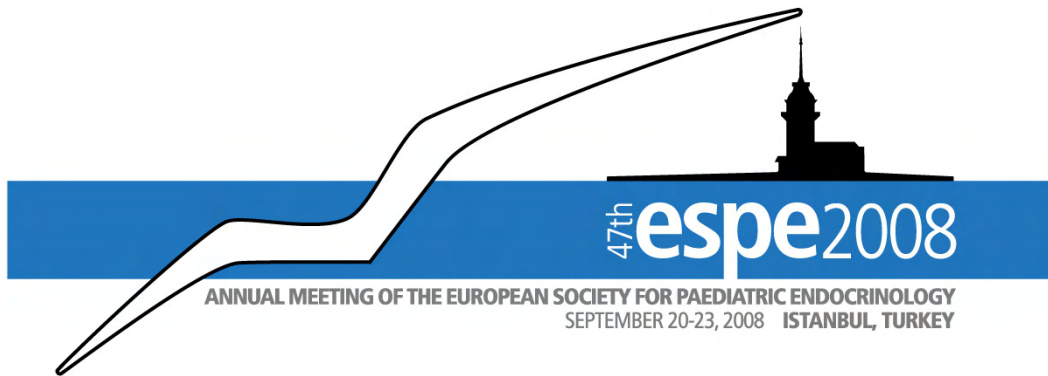
Two interesting clinical cases will be thoroughly discussed in an interactive form with all of the attendants. Physical exam, familial and personal antecedents, auxological, biochemical, image and molecular studies will be discussed. In addition, optional treatments when diagnosis is reached will be also discussed, reviewing the most recent concepts in the international scientific literature.

## Clinical and Biochemical Algorithm of Delayed Puberty



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## Meet the Expert Session

7:1 - 7:2

### Interpretation of endocrine tests

*Nurgün Kandemir, Ankara, Turkey*

Sunday September 21

13:30 - 14:30

Galata

15:15 - 16:15

Haliç



## What is next step?

### Case 3:

A 15.9 year old boy was admitted to our clinic with the complaint of short stature. He has always been short which was more striking after the age of 13 years, also his growth rate decreased when compared to his peers in the last 2 years. His birth weight was normal and he was otherwise healthy.

His father is 160 cm tall and mother 152 cm and his sister is 20 years old and 149.5 cm tall. The father remembers being short until high school years. The mother's menarche was at 13 years of age.

On physical examination;

Height 142cm (-4.28 SDS)

Weight for height 95th percentile

Body proportions and system findings are normal, he is at pubertal stage 2, testicular volumes are 4 ml, pubic hair stage 2 and no axillary hair.

Laboratory investigations revealed a bone age 12.5 years. Complete blood count, sedimentation, liver and kidney function tests, thyroid function tests were normal. Serum gonadotropin and testosterone levels were in the prepubertal range.

Serum IGF-1 level: 273.31 ng/ml

Serum IGFBP-3 level: 3161.07 ng/ml

Peak GH response was 3.21 ng/ml on L-DOPA stim. test

### Result of an insulin tolerance test

Time	Blood glucose	GH (ng/ml)	Cortisol ( $\mu\text{g}/\text{dl}$ )
0	63	1.01	27.4
15	24	0.91	31.1
30	68	2.93	45.2
45	86	3.83	41.2
60	95	1.66	40.0
90	97	1.24	38.6

## What is the best next step?

### Discussion

#### *Case 1 and 2 : Establishment of the diagnosis and cause of Cushing's Syndrome*

Establishment of the diagnosis of Cushing's syndrome (CS) takes several steps.

The first step is to determine if the patient has CS.

External glucocorticoid intake and pseudocushing syndrome due to stress, severe obesity, major depressive disorders should be excluded. There are guidelines for adults (fig 1). Most of the recommendations in childhood is based on the adult data. However there is no well established guideline in pediatric age group.

The initial tests used for screening include, 24 h urinary free cortisol, late night serum or salivary cortisol and 1 mg dxm. suppression test. Low dose dexametasone suppression test (LDDST) is also used for screening in adults. In children Dias et.al. showed that the degree of cortisol suppression during LDDST was predictive for cortisol suppression during HDSST. Therefore they suggested that the LDDST has diagnostic value in the establishment of the cause of CS.

In 105 children with CS it was shown that a midnight cortisol  $\geq 4.4\mu\text{g}/\text{dl}$  has 99% sensitivity and 100% specificity to establish the diagnosis. Also in that study overnight high dose dxm. suppression test diagnosed almost all patients with pituitary adenomas. The sensitivity and specificity was 97.5% and 100%.

Pituitary MRI is normal in up to 50% of adult patients and 60% of children with Cushing's disease and can be abnormal in 10% of healthy individuals. Although it can not be used for the identification of the patients with Cushing's disease, it should be done before inferior petrosal sinus sampling (IPSS) or surgery to exclude large tumor. In 3 studies with large groups of children with CS it was shown that IPSS is safe and well tolerated in the pediatric age group. Since ectopic ACTH release is very rare in children its use is mainly limited to the lateralization of the pituitary tumor. In adults the sensitivity of IPSS for lateralization was 60-90% before and after CRH administration. In children there are different results. One study claimed that it is a poor predictor for lateralization (58%) and the other showed that it is a reliable test for that (79%).

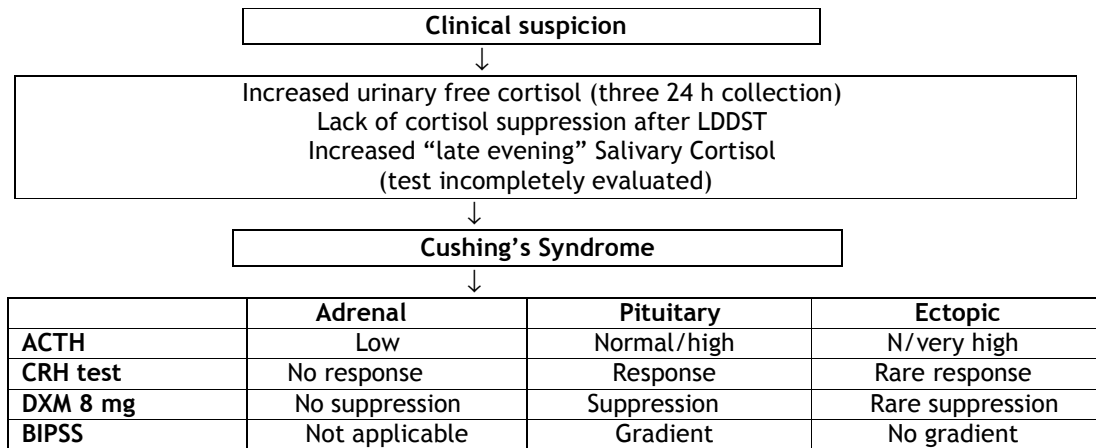


Figure 1. Guidelines for the diagnosis of CS

#### Discussion

##### Case 3.

The differential diagnosis of transient and permanent growth hormone (GH) deficiency is a real problem for some children near puberty. Re-evaluation of patients treated with GH revealed that 13.5-67% of them responded normal to GH stimulation tests following the cessation of therapy.

Priming with sex steroids prior to GH stimulation tests was shown to increase GH responses and it is used for differentiation of permanent and transient GH deficiency in children during peripubertal period.

However the use of priming is still controversial and previously in a survey it was shown that 67% of the respondents did not use priming prior to GH stimulation tests. One of the reasons for the controversy is the lack of data on the outcome of these children.

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