Investigation of

MALE REPRODUCTIVE HORMONE DYSFUNCTIONS

from diagnosis,
the seeds of better health
Precocious and delayed puberty
Hypogonadism
Gynecomastia
Azoospermia

The approach used for each of the subjects discussed in this booklet is identical:

• brief physiological description
• clinical approach
• basic biological profile
• interpretation of results
• secondary tests, if required
• treatment

Dynamic tests and a list of the main hormone assays are given at the end of the booklet.
Complete pubertal development takes 2 to 3 years.
It is preceded by an adrenal maturation phase (at the age of 7 or 8),
known as the adrenarche, biochemically characterized by an
increase in circulating DHEAS*.

* Dehydroepiandrosterone sulfate.
**precocious puberty**

**Onset of puberty before the age of 9**
(European population)

**CLINICAL SIGNS**
Growth of pubic hair, and possible signs of gynecomastia. Growth of testes and/or development of the penis and scrotum.

**INITIAL PROFILE**
This profile aims to differentiate between:
- central precocious puberty.
- primary precocious puberty or pseudoprecocious puberty.

**INTERPRETATION OF RESULTS**

<table>
<thead>
<tr>
<th>secondary sexual characteristics</th>
<th>2 small testes</th>
<th>Only 1 enlarged testis</th>
<th>2 enlarged testes</th>
</tr>
</thead>
<tbody>
<tr>
<td>basic FSH-LH levels</td>
<td>low</td>
<td>low</td>
<td>normal or increased</td>
</tr>
<tr>
<td>response to LH-RH test</td>
<td>prepubertal</td>
<td>prepubertal or low</td>
<td>pubertal</td>
</tr>
<tr>
<td>secondary tests for confirmation or orientation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• abdominal / pelvic radio-imaging techniques</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• normal testosterone or, DHEAS and Δ4, 17-OH-P</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>dynamic tests</td>
<td>ACTH test</td>
<td>Tumor of the testes</td>
<td>Central, idiopathic or neurogenic precocious puberty</td>
</tr>
<tr>
<td>• isolated pubic hair or precocious adrenarche</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Congenital adrenal hyperplasia</td>
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</tbody>
</table>

**TREATMENT**
Treatment of the tumor, if required.
In cases of true central precocious puberty, pubertal development is halted by using an LH-RH agonist (an annual LH-RH test controls the degree of pituitary blockage).

Treatment of congenital adrenal hyperplasia.
No growth of pubic hair, nor development of other secondary sexual characteristics.

**INITIAL PROFILE**

This profile aims to differentiate between:

- delayed puberty: hCG test.
- hypogonadotropic hypogonadism.
- hypergonadotropic hypogonadism.

It comprizes:

- an hCG test.
- basic FSH and LH levels + LH-RH test.
- Testosterone.
- DHEAS to evaluate adrenal maturation or adrenarche.
- evaluation of stature and bone age to orient a diagnosis of delayed puberty.

**CLINICAL SIGNS**

No signs of puberty after the age of 15 (European population)

**INTERPRETATION OF RESULTS**

<table>
<thead>
<tr>
<th>hCG test</th>
<th>normal response</th>
<th>insufficient or zero response</th>
</tr>
</thead>
<tbody>
<tr>
<td>basal FSH-LH levels</td>
<td>normal or low</td>
<td>normal or increased</td>
</tr>
<tr>
<td>response to LH-RH test</td>
<td>prepubertal</td>
<td>pubertal or increased response</td>
</tr>
</tbody>
</table>

**TREATMENT**

Substitutive (testosterone-based) for functional hypogonadotropic hypogonadism and some types of hypergonadotropic hypogonadism.
**CLINICAL SIGNS**
- decreased libido
- sexual indifference
- impotence
- physical fatigue
- reduced muscle mass
- reduced testicular volume

**INITIAL PROFILE**
Testosterone, FSH, LH, Prolactin, Inhibin B

**INTERPRETATION OF RESULTS**

<table>
<thead>
<tr>
<th><strong>Testosterone</strong></th>
<th><strong>Inhibin B</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>to (for info: Reference values = 3 to 12 ng/ml)</td>
<td>to</td>
</tr>
<tr>
<td>FSH and LH are normal</td>
<td></td>
</tr>
</tbody>
</table>

**ETIOLOGIES**

**SUPRASELLAR LESIONS**
- Tumoral (CT scan + NMR)
  - craniopharyngioma, visual disorders
  - and/or panhypopituitarism
  - germinoma, (hCG, AFP)
  - glioma of optic chiasm or hypothalamus
- Post-infectious
  - tuberculous meningitis
  - or other microorganism
- Infiltration processes (NMR necessary)
  - histiocytosis
  - sarcoidosis
- Post radiotherapy
- Section of the pituitary stalk

**PITUITARY ORIGIN**
- Hemochromatosis
  - ferritin > 1000 µg/l
  - investigation of C282Y mutation
  - gonadotropic cells affected by Fe deposition
  - no GnRH stimulation
- Hyperprolactinemia
  - Prolactin = strong antigonadotropic effect on the hypothalamus
  - Prolactin adenoma
    - (80% of pituitary adenomas)
- Secreting or non-secreting pituitary adenomas

**FUNCTIONAL DEFICIENCIES**
- Anorexia (rare in males)
- Nutritional disorders: celiac disease due to gluten intolerance
- Hypercorticism, long-term corticosteroid therapy
- Hyperestrogenemia
  - estrogen treatment (transvestites)
  - estradiol-secreting tumor

**TREATMENT**
- Pulsatile GnRH pump (1 to 2 years), if positive test response
- Long-term IM administration of testosterone
- Specific according to etiology
**Clinical Signs**

Unilateral or bilateral enlargement of the male breast (normally undeveloped)
- Newborn (due to placental estrogen)
- Puberty (60% of adolescents aged between 12 and 15)
- Adult: frequent, often asymptomatic, increasing incidence with age, occasionally with breast deformation and tenderness.

**Anamnesis:**
- hyperthyroidism
- renal insufficiency (dialysis)
- hepatic insufficiency
- therapeutic drugs or non-therapeutic substances *
- libido
- galactorrhea

**Initial Profile**

**Biological:**
Testosterone, Estradiol, hCG

**Radiological:**
mammography

hCG secretion may orient diagnosis towards a secreting choriocarcinoma or neoplasia (e.g. lung). Mammography should identify an increase in adipose tissue linked to obesity or breast cancer (rare).

**Interpretation of Results**

<table>
<thead>
<tr>
<th></th>
<th>Testosterone</th>
<th>Estradiol</th>
<th>FSH-LH</th>
<th>SHBG</th>
<th>Prolactin</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Testosterone-receptor deficiency</td>
<td>ANDROGEN RESISTANCE</td>
<td>PERIPHERAL HYPOGONADISM</td>
<td>HYPOGONADOTROPIC HYPOGONADISM</td>
<td>SECRETING ESTRADIOL TUMOR</td>
<td></td>
</tr>
<tr>
<td>Reifenstein’s syndrome</td>
<td>Primitive karyotype (Klinefelter’s syndrome)</td>
<td>Pituitary adenoma - with PRL secretion (galactorrhea) - other</td>
<td>Cirrhosis (Hepatic insufficiency)</td>
<td>Leydig cell tumor</td>
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</tr>
<tr>
<td>Cytosstatics and irradiation (testicular lesion)</td>
<td>Hyperprolactinemia drugs</td>
<td>Neuroleptics, tricyclical antidepressant drugs</td>
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</tr>
<tr>
<td>* Therapeutic drugs responsible for gynecomastia</td>
<td>- Estrogens</td>
<td>- Androgens, anabolic steroids (peripheral aromatizations)</td>
<td>- Spironolactone</td>
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<td></td>
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<td>- Androgens, anabolic steroids (peripheral aromatizations)</td>
<td>- Spironolactone</td>
<td>- Cimetidine</td>
<td>- hCG therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Spironolactone</td>
<td>- Cimetidine</td>
<td>- hCG therapy</td>
<td>- Antiandrogenic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cimetidine</td>
<td>- hCG therapy</td>
<td>- Antiandrogenic drugs</td>
<td>- Digitalis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- hCG therapy</td>
<td>- Antiandrogenic drugs</td>
<td>- Digitalis</td>
<td>- Isoniazid</td>
<td></td>
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<td>- Digitalis</td>
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*Non-therapeutic substances*

- Cannabis (marijuana)
- Heroin
- Estrogen-rich hair lotions
- Partner’s local estrogen therapy
  (« vacation gynecomastia »)
The diagnosis of azoospermia is based on the absence of spermatozoa.

**Clinical Signs**

The clinical approach takes into consideration:
- the size and consistency of the testes
- mental retardation
- pubic and axillary hair and muscle mass
- size of penis (micropenis)
- the possible existence of gynecomastia
- hypoandrim

**Reminder:** characteristics of a normal spermogram (histological viewpoint)
- Ejaculate volume > 2.5 ml
- Number of spermatozoa : > 20 million/ml
- Percentage of motile spermatozoa after 4 hrs > 60 %
- Percentage of morphologically normal forms 40 - 70 %
- Percentage of living forms (vitality) 60 - 90 %

**Initial Profile**

Involves FSH, LH and Testosterone

**Interpretation of Results**

Secondary tests for confirmation or orientation

<table>
<thead>
<tr>
<th>Testosterone (Hypogonadism)</th>
<th>Normal testosterone and LH levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>( FSH ), ( LH )</td>
<td>( FSH ) normal or ( LH ) normal or</td>
</tr>
<tr>
<td>Hypergonadotropic hypogonadism</td>
<td>Hypergonadotropic hypogonadism</td>
</tr>
<tr>
<td>• Barr test (+) and/or karyotype</td>
<td>• Biochemical study of sperm</td>
</tr>
<tr>
<td>• Barr test (-)</td>
<td>• Biopsy of the testes to confirm germinal insufficiency</td>
</tr>
</tbody>
</table>

**Klinefelter's syndrome (47,XXY)**

**Sequellae of testicular trauma (chemotherapy, radiotherapy)**

**Reminder:** characteristics of a normal spermogram (histological viewpoint)
- Ejaculate volume > 2.5 ml
- Number of spermatozoa : > 20 million/ml
- Percentage of motile spermatozoa after 4 hrs > 60 %
- Percentage of morphologically normal forms 40 - 70 %
- Percentage of living forms (vitality) 60 - 90 %
**LH-RH (or GnRH) TEST**

**Intravenous injection** at T₀ of 100 µg/m² (child) or 100 µg (adult) of LH-RH

**Assay** of FSH or LH at T₁₅, T₀, T₂₀, T₄₀, T₆₀, T₉₀ minutes

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**SYNACTHEN TEST (synthetic ACTH)**

**Intramuscular injection** at T₀ of 0.25 mg of Synacthen (0.125 mg if ≤ 2 years old),

**Assay** of cortisol, 17-OH-progesterone, aldosterone, DHEAS, 4-Androstenedione at T₀, T₃₀ and/or T₆₀ minutes.

An objective normal response is obtained if there is an increase in cortisol and aldosterone (minimum factor 2) without any significant modification of the other parameters.

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**hCG TEST**

**Intramuscular injection** on D₁, D₃, and D₅ of 1500 IU of hCG,

**Testosterone assay** on D₁ and D₆.

The testosterone level must be at least 3 ng/ml in prepubertal phase and may reach similar values to those of the adult (7 to 12 ng/ml) during puberty.
**BLOOD HORMONE ASSAYS:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIDAS hCG</td>
<td>30 405</td>
</tr>
<tr>
<td>VIDAS LH</td>
<td>30 406</td>
</tr>
<tr>
<td>VIDAS FSH</td>
<td>30 407</td>
</tr>
<tr>
<td>VIDAS Prolactin</td>
<td>30 410</td>
</tr>
<tr>
<td>VIDAS Progesterone</td>
<td>30 409</td>
</tr>
<tr>
<td>VIDAS Estradiol II</td>
<td>30 431</td>
</tr>
<tr>
<td>VIDAS Testosterone</td>
<td>30 418</td>
</tr>
<tr>
<td>VIDAS Cortisol</td>
<td>30 417</td>
</tr>
<tr>
<td>VIDIA hCG*</td>
<td>38 300</td>
</tr>
<tr>
<td>VIDIA LH*</td>
<td>38 310</td>
</tr>
<tr>
<td>VIDIA FSH*</td>
<td>38 320</td>
</tr>
<tr>
<td>VIDIA Prolactin*</td>
<td>38 330</td>
</tr>
<tr>
<td>VIDIA Progesterone*</td>
<td>38 340</td>
</tr>
<tr>
<td>VIDIA Estradiol*</td>
<td>38 350</td>
</tr>
</tbody>
</table>

Availability of some VIDAS tests may be restricted in certain countries due to registration requirements. Consult our local representatives for further information.

*In development.

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