Investigation of

FEMALE REPRODUCTIVE HORMONE DYSFUNCTIONS
Precocious and delayed puberty
Secondary amenorrhea
Hirsutism
Other pathologies: primary amenorrhea and hyperprolactinemia
Menopause

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 examinations, if required
• treatment

Dynamic tests and a list of the main hormone assays are given at the end of the booklet.
**Early Follicular Phase (D-3 to D5)**
- Selective follicular recruitment

**Late Follicular Phase**
- FSH/LH > 1
- Pre-ovulatory phase
- Androgens: 4-Androstenedione, Testosterone, ...
- PGE, PGF₂, IGF-I, Inhibin B
- Inhibin B
- Estradiol (E₂) ≤ 40 pg/ml

**Luteal Phase**
- LH receptor
- Corpus luteum
- Aromatase
- Progesterone
- 37°C

**Steroidogenesis**
- LH-dependent / Aromatization: FSH-dependent

**Hormonal Physiology**
- LH: Luteinizing Hormone
- FSH: Follicle-Stimulating Hormone
- GnRH: Gonadotropin Releasing Hormone
- IGF: Insulin-like Growth Factor
- PGE, PGF: Prostaglandins

**Hormone Secretions**
- Estradiol
- Progesterone

**Temperature Curve**
- Follicular phase
- Peri-ovulatory phase
- Luteal phase
Onset of puberty before the age of 8 (European population).

**CLINICAL SIGNS**
Breast development and/or growth of pubic and axillary hair.

**INITIAL PROFILE**
This profile aims to differentiate between:

- isolated pubic and axillary hair growth (pubarche)
- isolated breast development (thelarche)
- central precocious puberty
- primary precocious puberty (pseudoprecocious puberty)

It comprises:

- basic FSH and LH levels + LH-RH test (GnRH)
- Estradiol
- DHEAS to evaluate adrenal maturation or adrenarche
- evaluation of stature and bone age

**INTERPRETATION OF RESULTS**

<table>
<thead>
<tr>
<th>secondary sexual characteristics</th>
<th>Isolated or predominant breast development</th>
<th>Predominant or isolated axillary hair growth</th>
<th>More or less balanced development</th>
</tr>
</thead>
<tbody>
<tr>
<td>basic FSH-LH levels</td>
<td>FSH low</td>
<td>LH normal or low</td>
<td>normal or increased</td>
</tr>
<tr>
<td>response to LH-RH test</td>
<td>FSH prepubertal or low</td>
<td>LH prepubertal</td>
<td>pubertal</td>
</tr>
<tr>
<td></td>
<td><strong>PREOCIOUS THELARCHE</strong></td>
<td><strong>isor rental or isolated axillary hair</strong></td>
<td><strong>More or less balanced development</strong></td>
</tr>
<tr>
<td></td>
<td><strong>OVARIAN PRIMARY PREOCIOUS PUBERTY</strong></td>
<td><strong>OVARIAN PRIMARY PREOCIOUS PUBERTY</strong></td>
<td><strong>TRUE PREOCIOUS PUBERTY (OR CENTRAL)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>CENTRAL NEUROGENIC OR IDIOPATHIC PREOCIOUS PUBERTY</strong></td>
<td><strong>CENTRAL NEUROGENIC OR IDIOPATHIC PREOCIOUS PUBERTY</strong></td>
<td><strong>TREATMENT</strong></td>
</tr>
</tbody>
</table>

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

Complete pubertal development takes 2 to 3 years. It is preceded by an adrenal maturation phase (at the age of 6 or 7) known as the adrenarche, biochemically characterized by an increase in circulating DHEAS*.

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*Dehydroepiandrosterone sulfate.*
**CLINICAL SIGNS**

No signs of puberty after the age of 13 - 14 (European population).

**INITIAL PROFILE**

No breast development, nor pubic and axillary hair growth.

This profile aims to differentiate between:

- delayed puberty
- hypogonadotropic hypogonadism
- hypergonadotropic hypogonadism

**INTERPRETATION OF RESULTS**

<table>
<thead>
<tr>
<th>Secondary sexual characteristics</th>
<th>No breast development</th>
<th>No pubic and axillary hair growth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic FSH-LH levels</strong></td>
<td>Normal or low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Response to LH-RH test</strong></td>
<td>Prepubertal</td>
<td>Low even nil</td>
</tr>
<tr>
<td></td>
<td>Pubertal or increased</td>
<td>response</td>
</tr>
</tbody>
</table>

- **Delayed Puberty 1 in every 5 cases**
- **Hypogonadotropic Hypogonadism**
- **Hypergonadotropic Hypogonadism**

**Secondary examinations for confirmation or orientation**

- Cerebral radio-imaging techniques
- GH, TSH, Cortisol, 4-Androstenedione
- Panhypopituitarism (congenital or acquired)
- Isolated gonadotropic insufficiency
- Panhypopituitarism (congenital or acquired)
- Isolated gonadotropic insufficiency
- Specific genetic disorder (e.g. Testicular Feminization Syndrome)
- Miscellaneous causes:
  - Visceral or general (e.g. chronic renal failure)
  - Endocrinopathy (e.g. hypothyroid, hypercortisolism)
  - Psychological or social (e.g. anorexia)
- Panhypopituitarism (congenital or acquired)
- Isolated gonadotropic insufficiency
- Turner’s syndrome

**TREATMENT**

Substitutive (estrogen then estrogen-progestrone), except in cases of delayed puberty.
**CLINICAL SIGNS**
- No specific clinical signs
- No menses for over 3 months

**Anamnesis:**
Date of last childbirth, variation in weight, drugs, genital and breast examination, stop estrogen-progesterone treatment, affective shock...

**Background history of:**
- Chemotherapy and radiotherapy.
- Surgery (ectopic pregnancy, ovariectomy, appendectomy...).
- Infection (salpingitis, STD, tuberculosis)

**INITIAL PROFILE**

Firstly:
➢ Assay hCG to exclude pregnancy
   - If hCG negative, make an appointment in 1 to 2 weeks time using a menothermal curve (to exclude pregnancy or trophoblastic tumor)

Then:
➢ FSH, Estradiol, (LH)
➢ Prolactin (PRL)
➢ TSH if apathy and/or weight gain.

Hypothyroidism (increased TSH) leads to an increase in TRH which stimulates PRL secretion.

**INTERPRETATION OF RESULTS**

<table>
<thead>
<tr>
<th>hCG: negative</th>
<th>TSH: normal or regulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRL</td>
<td>FSH</td>
</tr>
<tr>
<td>increased</td>
<td>normal</td>
</tr>
<tr>
<td>E₂ ≥40 pg/ml</td>
<td>normal or low</td>
</tr>
<tr>
<td>initial profile if after halting treatment:</td>
<td>Progesterone test</td>
</tr>
<tr>
<td>PRL</td>
<td>- Early ovarian insufficiency?</td>
</tr>
<tr>
<td>• Iatrogenous origin</td>
<td>• Adenoma (radio-imaging techniques of the sella turcica and visual field)</td>
</tr>
<tr>
<td>• Estradiol to evaluate ovocytic maturation</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>(bleeding)</td>
<td>(no bleeding)</td>
</tr>
</tbody>
</table>

**Etiologies**
- Infection
- Endometrium lesion (following curettage)
- Physical / Psychological trauma (central amenorrhea)
- Sport at competitive level
- Adenoma / adrenal tumor or secreting ovary?
- E₂, Cortisol, Testo
- Recent non-secreting pituitary adenoma
- Hemorrhagic childbirth (Sheehan’s syndrome)

**Depending on etiology**
- Hysteroscopy
- Laparoscopy
- Endometrium, cervix biopsy
- Pelvic radio-imaging techniques
- Scan, NMR

**Basic tests**

**Secondary examinations for confirmation and orientation**

**Additional investigations and/or action to be taken:**
**Either desire for pregnancy:**
- FSH, LH, E₂
- Ovulation induction

**Or wait:**
- For menses to return
- FSH and LH control
- Cyclic progesterone treatment, if required
**Clinical Signs**

- Hirsutism: excess hair growth in regions stimulated by sexual hormones. Possible to grade (0 to 4) the level of excess hair. Hirsutism is pathological while hypertrichosis is ethnic and family-related.
- Acne, seborrhea
- Possible obesity (android fat distribution?)
- Recent signs of virilization (voice deepening, clitoromegaly...)

**Initial Profile** (before D5 if spaniomenorrhea)

This profile aims to distinguish:

- The origin of hyperandrogenemia (ovarian, adrenal or idiopathic).

Cases of recent virilization may also be of tumor origin, for which biological diagnosis must be rapid.

**Interpretation of Results**

<table>
<thead>
<tr>
<th>Test</th>
<th>N</th>
<th>N or</th>
<th>N or &gt;1</th>
<th>non informative</th>
<th>N or &gt;1</th>
<th>non informative</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>N</td>
<td>N</td>
<td>N or &gt;1</td>
<td>non informative</td>
<td>N</td>
<td>non informative</td>
</tr>
<tr>
<td>LH</td>
<td>N</td>
<td>N</td>
<td>N or &gt;1</td>
<td>non informative</td>
<td>N</td>
<td>non informative</td>
</tr>
<tr>
<td>LH/FSH ratio</td>
<td>&gt;2</td>
<td>N</td>
<td>N or &gt;1</td>
<td>non informative</td>
<td>N</td>
<td>non informative</td>
</tr>
<tr>
<td>4-Androstenedione</td>
<td>N or</td>
<td>N or &gt;1</td>
<td>N or &gt;1</td>
<td>non informative</td>
<td>N</td>
<td>non informative</td>
</tr>
<tr>
<td>Testosterone</td>
<td>N or</td>
<td>N or &gt;1</td>
<td>N or &gt;1</td>
<td>non informative</td>
<td>N</td>
<td>non informative</td>
</tr>
<tr>
<td>DHEAS</td>
<td>N</td>
<td>N</td>
<td>N or &gt;1</td>
<td>non informative</td>
<td>N</td>
<td>non informative</td>
</tr>
<tr>
<td>PRL</td>
<td>N</td>
<td>N</td>
<td>N or &gt;1</td>
<td>non informative</td>
<td>N</td>
<td>non informative</td>
</tr>
<tr>
<td>E2</td>
<td>N</td>
<td>N</td>
<td>N or &gt;1</td>
<td>non informative</td>
<td>N</td>
<td>non informative</td>
</tr>
<tr>
<td>17-OH-P</td>
<td>N</td>
<td>N</td>
<td>N or &gt;1</td>
<td>non informative</td>
<td>N or &gt;1</td>
<td>non informative</td>
</tr>
</tbody>
</table>

**Dynamic tests**

- LH-RH test: LH normal
- ACTH test: N 17-OH-P > 5 mg/ml at T0 + 60 mins

**Radio-imaging techniques**

- Ovarian cysts: Normal ovaries
- Adrenal volume

**PCO**

- Polycystic ovarian syndrome
- Biopathic hirsutism, hyperproduction and hyperconsumption of androgens, 5α-reductase-receptor disease
- Late appearance of adrenal hyperplasia (21-hydroxylase deficiency)
- Specific investigation of adrenocortical hyperfunction (Cushing's syndrome)

**Virilizing ovarian tumor**

N = reference value
Primary Amenorrhea

Secondary sexual characteristics are most often absent (impuberty)

- external genital organs (pubic hair, vulva, clitoris) not or only slightly developed
- internal genital organs (vagina, uterus, hymen, ovaries) normal or more or less absent

Initial profile

FSH, LH, E₂

Interpretation of Results

Basic tests

<table>
<thead>
<tr>
<th>FSH↑↑, LH↑↑, E₂↑↑</th>
<th>FSH, LH = N or E₂ low</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPERGONADOTROPIC HYPOGONADISM</td>
<td>HYPOGONADOTROPIC HYPOGONADISM</td>
</tr>
</tbody>
</table>

Secondary examinations for confirmation or orientation

- sex chromatin (jugal mucous)
- karyotype

- 46XY
- 46X0
- Turner’s syndrome
- 17-α-hydroxylase deficiency
- Savvy-James syndrome
- Testicular Feminizing syndrome
- Savoy-James syndrome
- Testicular Feminizing syndrome

FSH↑ or N

LH↑

Text type
- Minimum breast development
- Abdominal or inguinal testicles
- androgen insensitivity (no DHT-receptors)

- 46XX
- 46XX
- Kallman’s syndrome
- Prader-Willi’s syndrome
- Functional: congenital disease, chronic disease (IRC…), anorexia
- hypothalamic origin
- hypothalamic origin

- LH-RH test
- pituitary origin
- infiltration disease, sarcoidosis, histiocytosis
- Tumors: cranial-pharyngioma, glioma, adenoma

Other pathologies

- Turner’s syndrome
- 46X0
- 90% of cases

Clinical signs

Initial profile

Interpretation of results
**OTHER PATHOLOGIES**

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**PHYSIOLOGICAL ROLE - REGULATION**

Prolactin (= lactotropic hormone) is a peptide hormone

**Role:** triggering and maintaining lactation

**Secretion** by the pituitary according to a circadian rhythm

(max.: between 2 am and 6 am; min.: 10 am and 12 pm)

**Regulation:**
- inhibition of secretion by hypothalamic Dopamin
- stimulation of secretion by TRH (see dynamic tests page 21)
- other factors increase secretion: stress, thyroid hormones, corticoids, estrogens, physical exercise, meals and some therapeutic drugs (see below).

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**INITIAL PROFILE**

**Precautions when assaying Prolactin:**

- rest (no stress)
- detailed questioning: dates of last menses, intensive sport, treatment in progress...

**Indicative reference values:**

- men and children: < 15 ng/ml
- menstruating women: < 5 ng/ml
- menopausal women: < 20 ng/ml
- pregnant women: progressive increase until childbirth

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**INTERPRETATION OF RESULTS**

**Hypoprolactinemia**

There is no hyposecretion threshold; low levels have no clinical significance.

**Hyperprolactinemia**

In cases of primary hyperprolactinemia, treatment using Dopamin agonist and / or surgery.

**Therapeutic drugs causing hyperprolactinemia (examples)**

- Psychotropic drugs
- Antidepressant drugs
- Estrogens
- Metoclopramide
- Opium-based drugs
- Cimetidine
- Romitidine

---

**TREATMENT**

In cases of primary hyperprolactinemia, treatment using Dopamin agonist and / or surgery.

**Therapeutic drugs causing hyperprolactinemia (examples)**

- Psychotropic drugs
- Antidepressant drugs
- Estrogens
- Metoclopramide
- Opium-based drugs
- Cimetidine
- Romitidine
**Clinical Signs**

**Perimenopause**: physiological situation as of 45 - 50 yrs of age, with irregular or shorter cycles: follicular phase increasingly shorter (FSH, E₂), then luteal insufficiency with P₄ and LH which stimulates E₂.

Accompanying clinical signs: mastodynia, abdominal and pelvic distension, weight gain, irritability, hot flushes.

**Confirmed menopause**: estrogen levels markedly reduced (no menses for over one year).

**Early menopause**: after surgical or chemical castration, irradiation, chemotherapy, intense stress, affective shock, pituitary adenoma, pituitary neurosurgery...

**Confirmed menopause**: E₂, FSH, LH

**Initial Profile**

**Perimenopause**: FSH before D5 (decrease of follicular stock).

**Confirmed menopause**: FSH (≤30 IU/l)

**Treatment and/or Follow-up**

The strong hormonal instability (both intra- and inter-individual) most often requires progesterone treatment until menstruation stops.

**Substitutive hormone treatment**

- Quality of life
- Prevention of heart and cardio-vascular disease
- Prevention from the risk of osteoporosis
- Evaluation of the benefits to the heart and bones versus the risk of breast cancer

**Biological monitoring of substitutive hormone treatment**

- If required, E₂ to adapt the posology if percutaneous substitutive hormone treatment
- FSH (<30 IU/l)
- Carbohydrate-lipid profile annually or every 2 yrs.

Essentially clinical and radiological monitoring (mammography, ultra-sound scan).
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 T-15, T0, T20, T40, T60, T90 minutes

L-DOPA OR TRH TEST

Production of Prolactin is
- reduced by L-dopa
  Assay of PRL at T0, T15, T30, T60, T90 and T120 minutes
  maximum slowing down at T60 or T90
- stimulated by TRH
  Assay of PRL at T0, T15, T30, T60, T90 and/or T120 minutes
  increase of 200 to 300% between T15 and T60

SYNACTHEN TEST (SYNTHETIC ACTH)

Intramuscular injection of 0.25 mg of Synacthen at T0 (0.125 mg if ≤ 2 yrs 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.
**BLOOD HORMONE ASSAYS:**

VIDAS hCG .......................... ref. 30 405
VIDAS LH ............................ ref. 30 406
VIDAS FSH ............................ ref. 30 407
VIDAS Prolactin ................... ref. 30 410
VIDAS Progesterone .............. ref. 30 409
VIDAS Estradiol II ............. ref. 30 431
VIDAS Testosterone .......... ref. 30 418
VIDAS Cortisol .................. ref. 30 417

VIDIA hCG* ........................ ref. 38 300
VIDIA LH* .......................... ref. 38 310
VIDIA FSH* ........................ ref. 38 320
VIDIA Prolactin* .............. ref. 38 330
VIDIA Progesterone* ........ ref. 38 340
VIDIA Estradiol* ............. ref. 38 350

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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FERTILITY

Investigation of FEMALE REPRODUCTIVE HORMONE DYSFUNCTIONS

from diagnosis, the seeds of better health