FERTILITY

Investigation of

FEMALE REPRODUCTIVE HORMONE DYSFUNCTIONS

from diagnosis,
the seeds of better health

BIOMÉRIEUX

contents

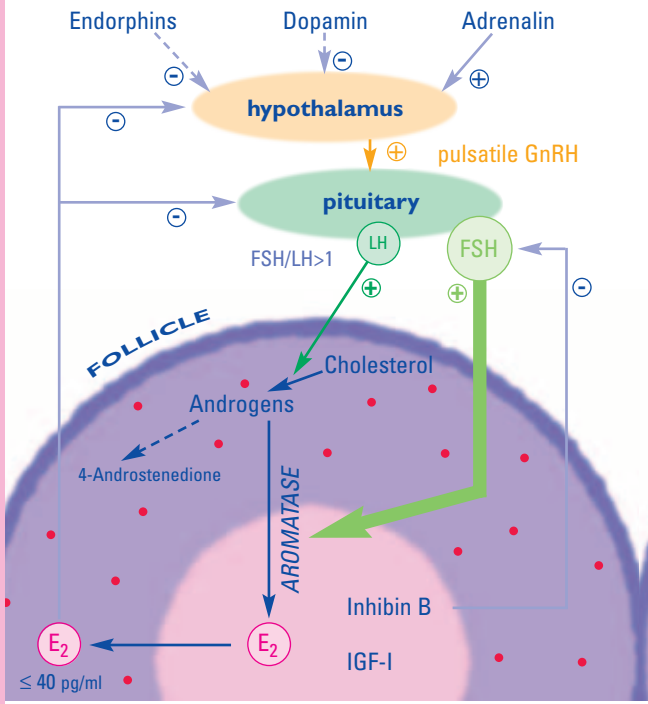
The approach used for each of the subjects discussed in this booklet is identical :

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

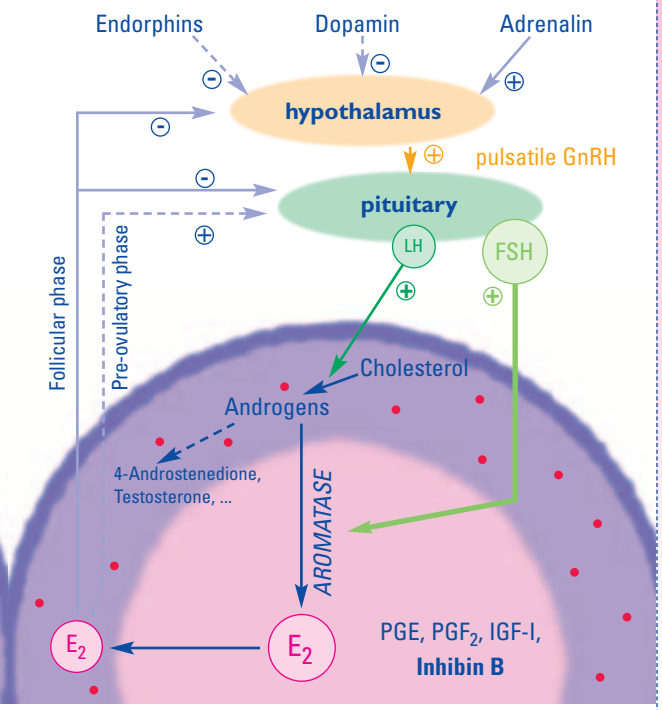
Dynamic tests and a list of the main hormone assays are given at the end of the booklet.

early follicular phase

D-3 ➪ D5 = selective follicular recruitment

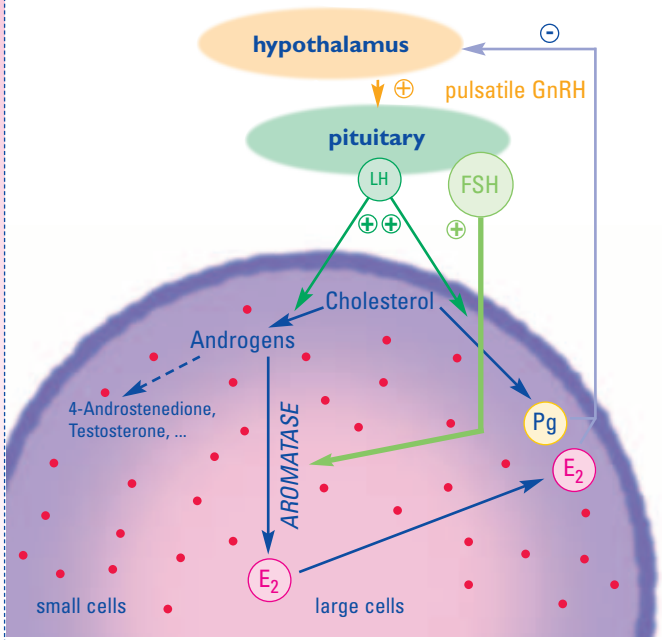


late follicular phase



OVULATION

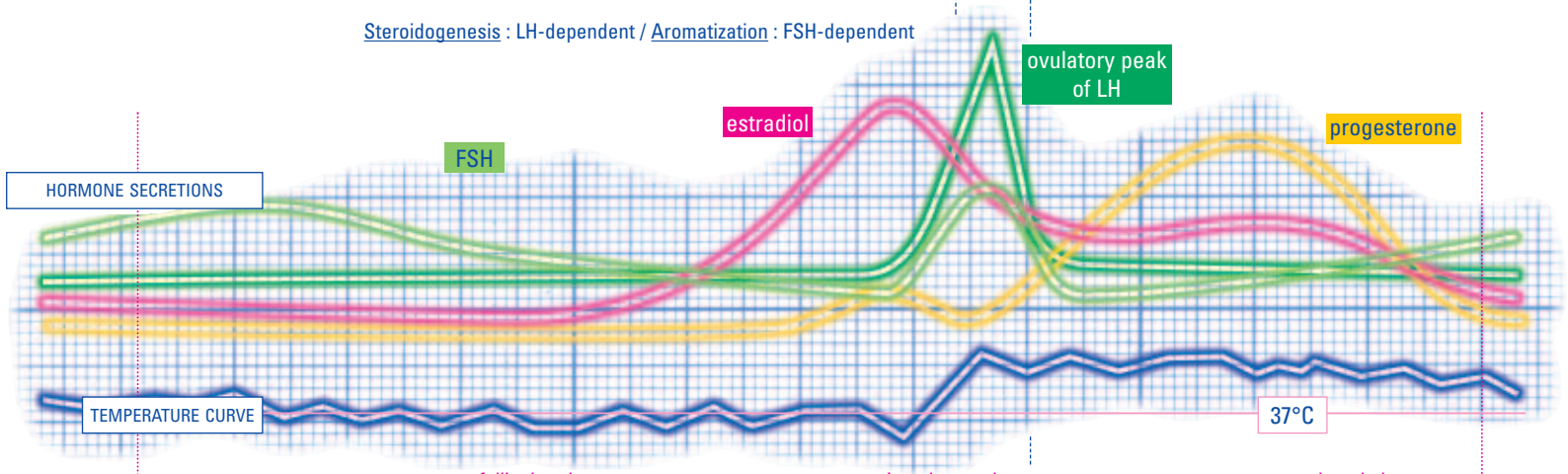
luteal phase



theca interna
theca externa
vascularization
granulosa cells

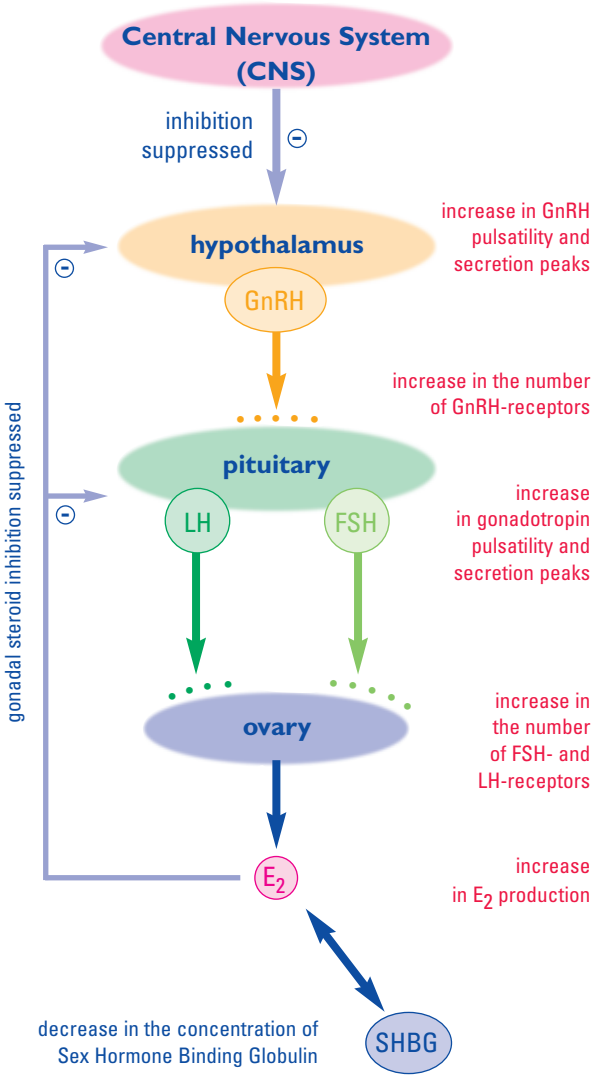
E_2 ..... Estradiol
Pg ..... Progesterone
GnRH ..... Gonadotropin Releasing Hormone
FSH, LH ... Gonadotropins
IGF ..... Insulin-like Growth Factor
PGE, PGF .. Prostaglandins

Steroidogenesis : LH-dependent / Aromatization : FSH-dependent



puberty

biochemical mechanisms



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*.

*Dehydroepiandrosterone sulfate.

precocious puberty

Onset of puberty before the age of 8
(European population).

Clinical signs

Breast development and/or growth of pubic and axillary hair.

Initial profile

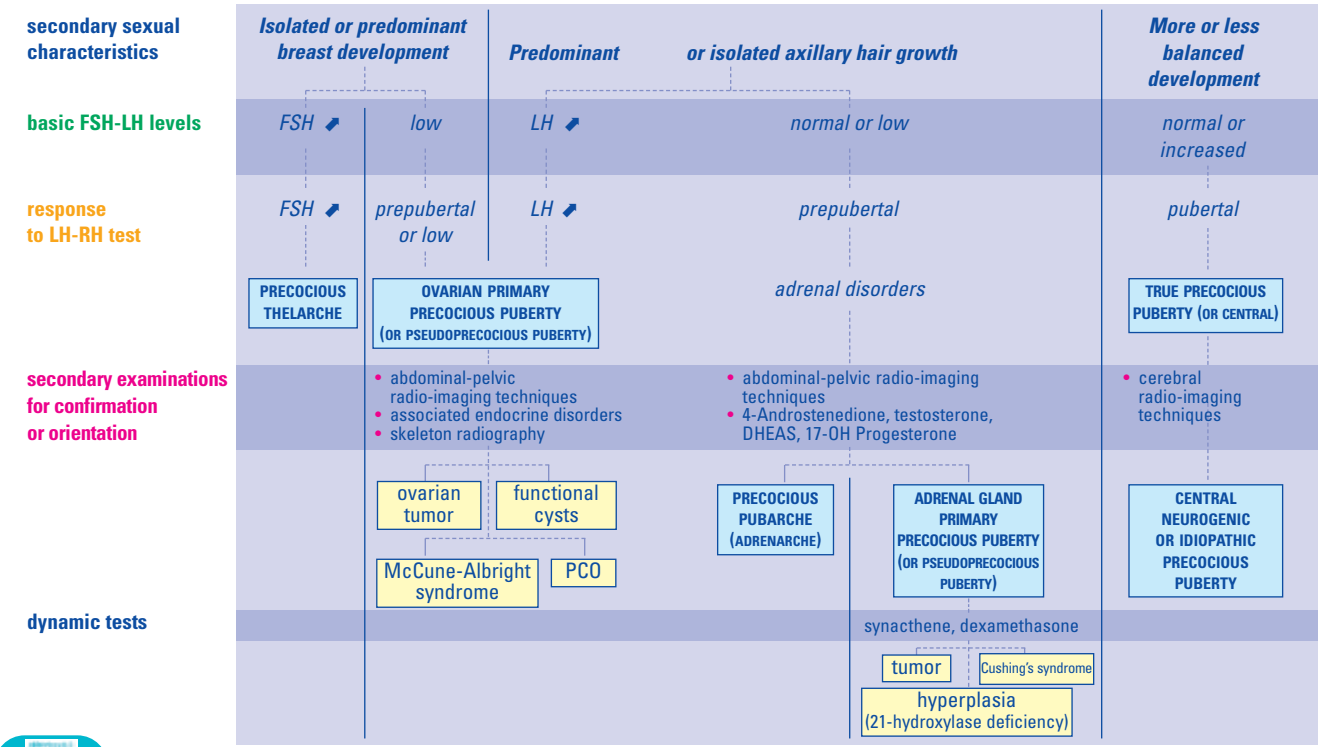
This profile aims to differentiate between :

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

It comprizes :

- 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



Treatment

- 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.

delayed puberty

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

Clinical signs

No breast development, nor pubic and axillary hair growth.

Initial profile

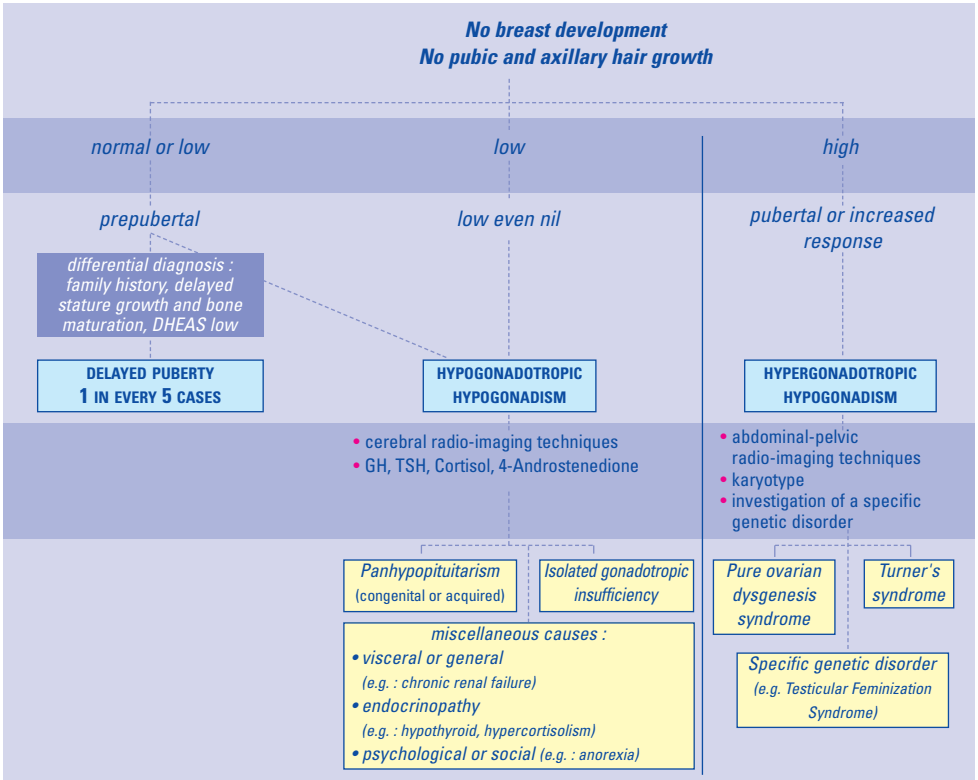
This profile aims to differentiate between :

- delayed puberty
- hypogonadotropic hypogonadism
- hypergonadotropic hypogonadism

It comprizes :

- basic FSH and LH levels + LH-RH test (GnRH)
- Estradiol
- DHEAS to evaluate adrenal maturation or adrenarche
- evaluation of stature and bone age for orientation of diagnosis to delayed puberty
- assay of prolactin to eliminate hyperprolactinemia

Interpretation of Results



Treatment

substitutive (estrogen then estrogen-progestrone), except in cases of delayed puberty.

secondary amenorrhea

(without hirsutism) Women < 46 yrs old

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, appendicectomy...).
- 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

hCG : negative
TSH : normal or regulated

Basic tests

PRL

increased — initial profile if after halting treatment : PRL ⬈⬈

normal — E_2 ≥40 pg/ml — Progesterone test

- Positive (bleeding) — Additional investigations and/or action to be taken :
  Either desire for pregnancy :
  - FSH, LH, E_2
  - Ovulation induction
  Or wait :
  - For menses to return
  - FSH and LH control
  - Cyclic progesterone treatment, if required
- Negative (no bleeding) — **Etiologies**
  - Infection
  - Endometrium lesion (following curettage)
  - Physical / Psychological trauma (central amenorrhea)
  - Sport at competitive level
  - Adenoma / adrenal tumor or secreting ovary ? E_2, 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

FSH

normal or low — Estradiol to evaluate ovocytic maturation (early menopause : "normal" or highly fluctuating levels of E_2)

increased — - early ovarian insufficiency ?
- anti-ovarian Ab ?

secondary examinations for confirmation and orientation

- iatrogenous origin
- adenoma (radio-imaging techniques of the sella turcica and visual field)

Clinical signs

No menses for over 3 months or 2 to 4 cycles per year.

- 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...)

Anamnesis :
- date of puberty - regularity of menses
- weight gain
- evolution of hirsutism - treatment in progress
- menothermic curves

Initial profile (before D5 if spaniomenorrhea)

This profile aims to distinguish :

➢ the origin of hyperandrogenia (ovarian, adrenal or idiopathic).

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

It comprizes :

➢ FSH, LH, Prolactin (PRL),
➢ Testosterone (T), E_2, 4-Androstenedione ($\Delta 4$), DHEAS, 17-OH-Progesterone (17-OH-P)
➢ Free cortisol in urine

Interpretation of Results

FSH	N	N	N	N	N
LH	↗↗	N or ↗	N or ↗	N or ↗	N
LH/FSH ratio (before D5) N<1	>2	N	N or >1	non informative	non informative
4-Androstenedione	↗↗	N or ↗	N or ↗	↗	↗↗↗
Testosterone	N or ↗	N or ↗ bio-available T ↗	N greater or ↗	N	↗↗
DHEAS	N or ↗	N	↗	↗	N
free cortisol in urine/creatinine ratio	N	N	N	↗↗	N
PRL	N or ↗	N	N	N	N
E_2	↗	N	non informative	non informative	↗
17-OH-P	N	N	N greater or ↗	↗	N or ↗
	PCO Polycystic ovarian syndrome	Idiopathic hirsutism, hyperproduction and hyperconsumption of androgens, 5-α-reductase-receptor disease	Late appearance of adrenal hyperplasia (21-hydroxylase deficiency)	Specific investigation of adrenocortical hyperfunction (Cushing's syndrome)	Virilizing ovarian tumor
Dynamic tests					
LH-RH test	LH ↗↗ FSH normal	N	N		
ACTH test	-	N	17-OH-P > 5 ng/ml at T_0 + 60 mins		-
Radio-imaging techniques	Ovarian cysts	Normal ovaries	Adrenal volume ↗		- scan, NMR - ovarian vein sampling : assay of T and $\Delta 4$ for each ovary

N = reference value

primary amenorrhea

adolescents, young women

Clinical signs

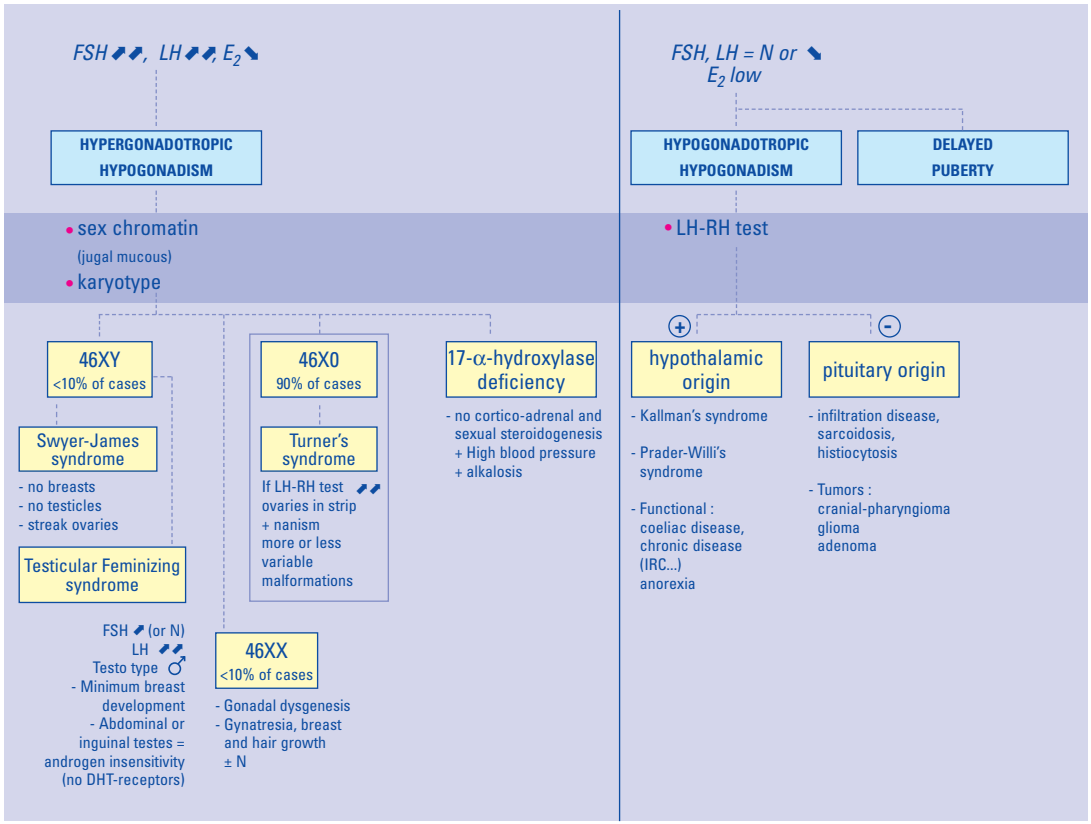
Secondary sexual characteristics are most often absent (impuberty)

- 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, E_2

Interpretation of Results



hyperprolactinemia

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 20)

other factors increase secretion : stress, thyroid hormones, corticoids, estrogens, physical exercise, meals and some therapeutic drugs (see below).

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 : < 25 ng/ml
menopausal women : < 20 ng/ml
pregnant women : progressive increase until childbirth

Interpretation of Results

Hypoprolactinemia

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

Hyperprolactinemia

	primary	secondary	functional	biological
clinical signs	cephalea, amenorrhea, galactorrhea		infertility, menstruating disorders	no clinical or radiological signs
basic prolactin	> 120 ng/ml	50 - 100 ng/ml	approx. 50 ng/ml	> 30 ng/ml
response to TRH test	no response			
secondary examinations	CT Scan, NMR			Chromatography of different circulating PRL forms
diagnosis	pituitary micro or macroadenoma	hypothalamus control suppressed due to tumor lesion, or post radiotherapy or sarcoidosis	following endocrine pathologies : hypothyroidism, **PCO**....	secretion of a minor form of PRL : **BIG-BIG Prolactin** ; no pathology

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 ⬈, E_2 ⬊), then luteal insufficiency with Pg ⬊ and LH ⬈
which stimulates E_2.
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...

Initial profile

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

Confirmed menopause : E_2 ⬊⬊, FSH ⬈⬈, LH ⬈

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

Short- and long-term beneficial effects :
- 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

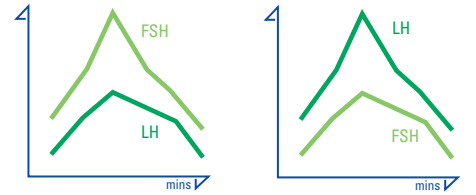
Biological monitoring of substitutive hormone treatment

- If required, E_2 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 T_0 , of 100 µg/m² (child)
or 100 µg (adult) of LH-RH

Assay of FSH or LH at T_{-15} , T_0 , T_{20} , T_{40} , T_{60} , T_{90} minutes



prepubertal type response

pubertal type response

L-DOPA OR TRH TEST

Production of Prolactin is

• reduced by L-dopa
Assay of PRL at T_0 , T_{15} , T_{30} , T_{60} , T_{90} and T_{120} minutes
maximum slowing down at T_{60} or T_{90}

• stimulated by TRH
Assay of PRL at T_0 , T_{15} , T_{30} , T_{60} , T_{90} and /or T_{120} minutes
increase of 200 to 300% between T_{15} and T_{60}

SYNACTHEN TEST (SYNTHETIC ACTH)

Intramuscular injection of 0.25 mg of Synacthen at T_0
(0.125 mg if ≤ 2 yrs old).

Assay of cortisol, 17-OH-progesterone, aldosterone,
DHEAS, 4-Androstenedione at T_0, T_{30} and/or T_{60} 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.

This booklet was created in collaboration with :

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