



## 10th International Conference and Scientific Symposium

*October 4-9, 2023*

*Sheraton North Baltimore Hotel*

# Endocrine Issues in Alstrom Syndrome

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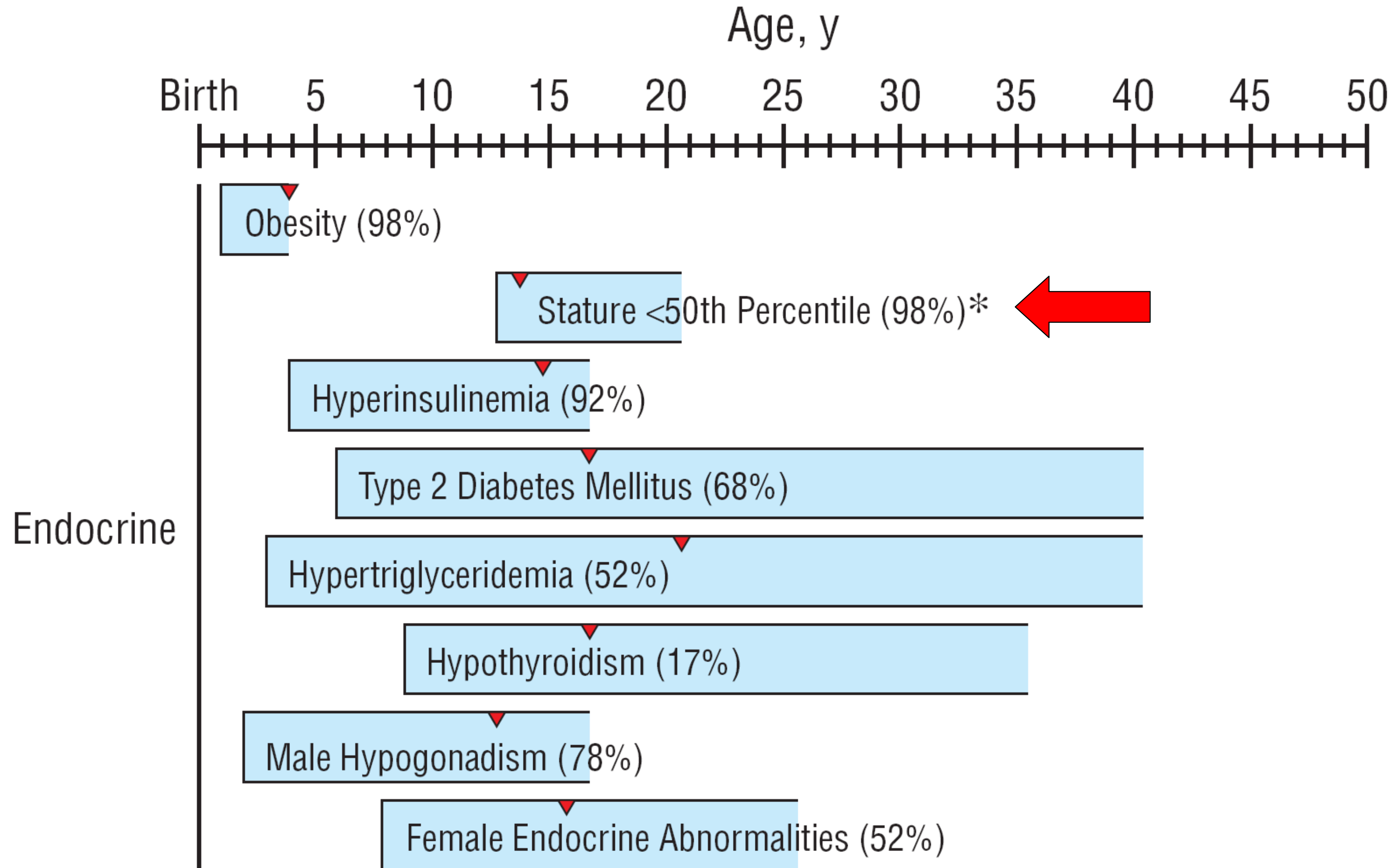
Endo-ERN

European Reference Network  
on Rare Endocrine Conditions

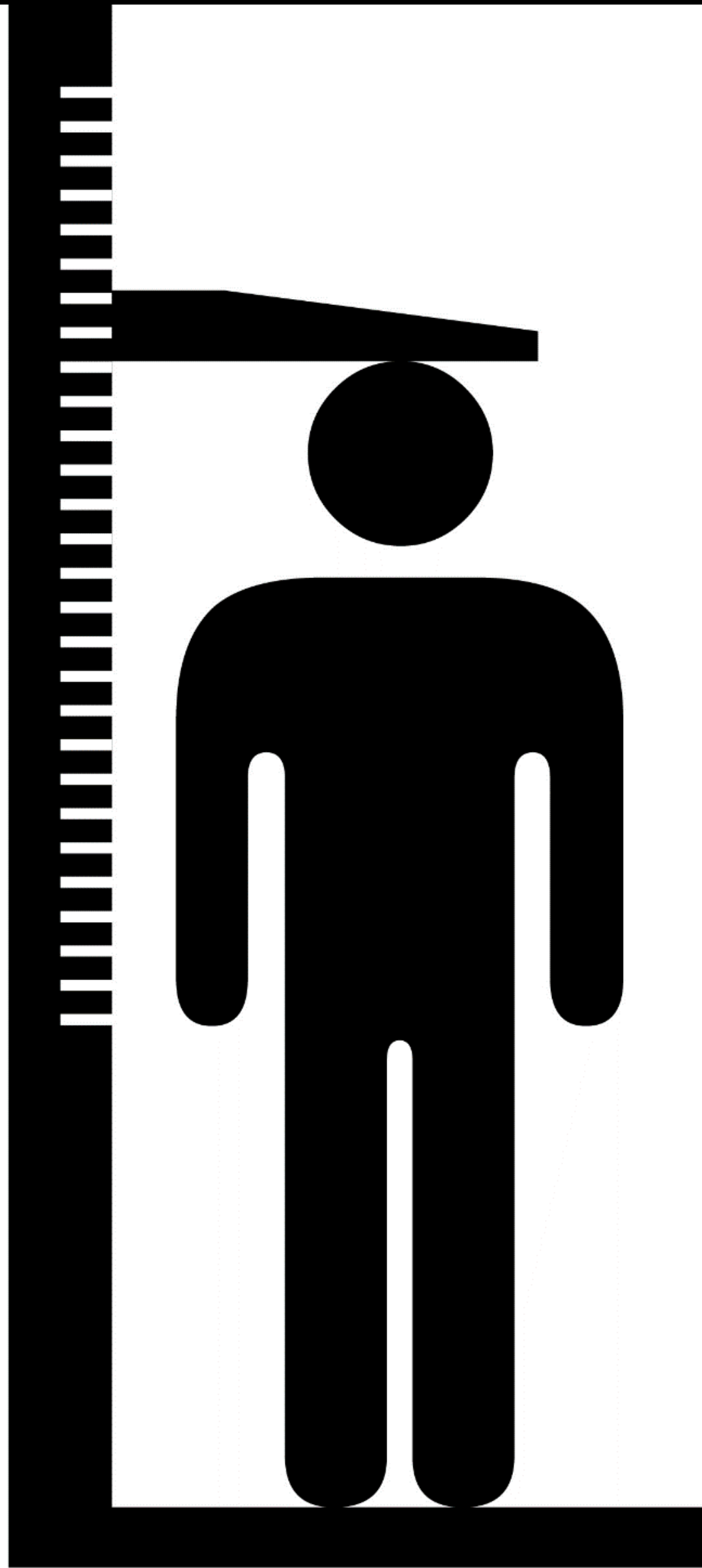
ASS.A.I. ONLUS



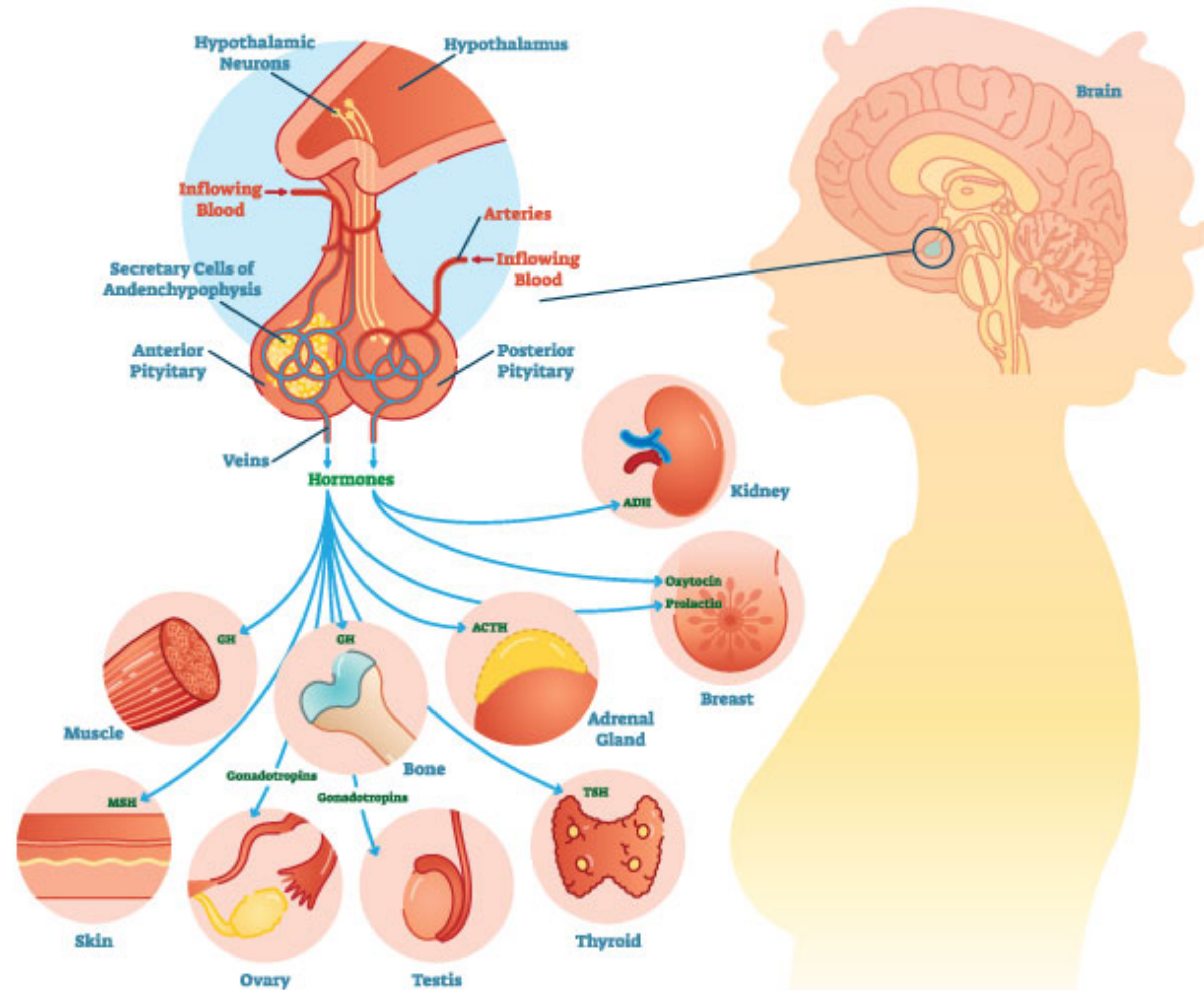
# Clinical Features – 182 patients



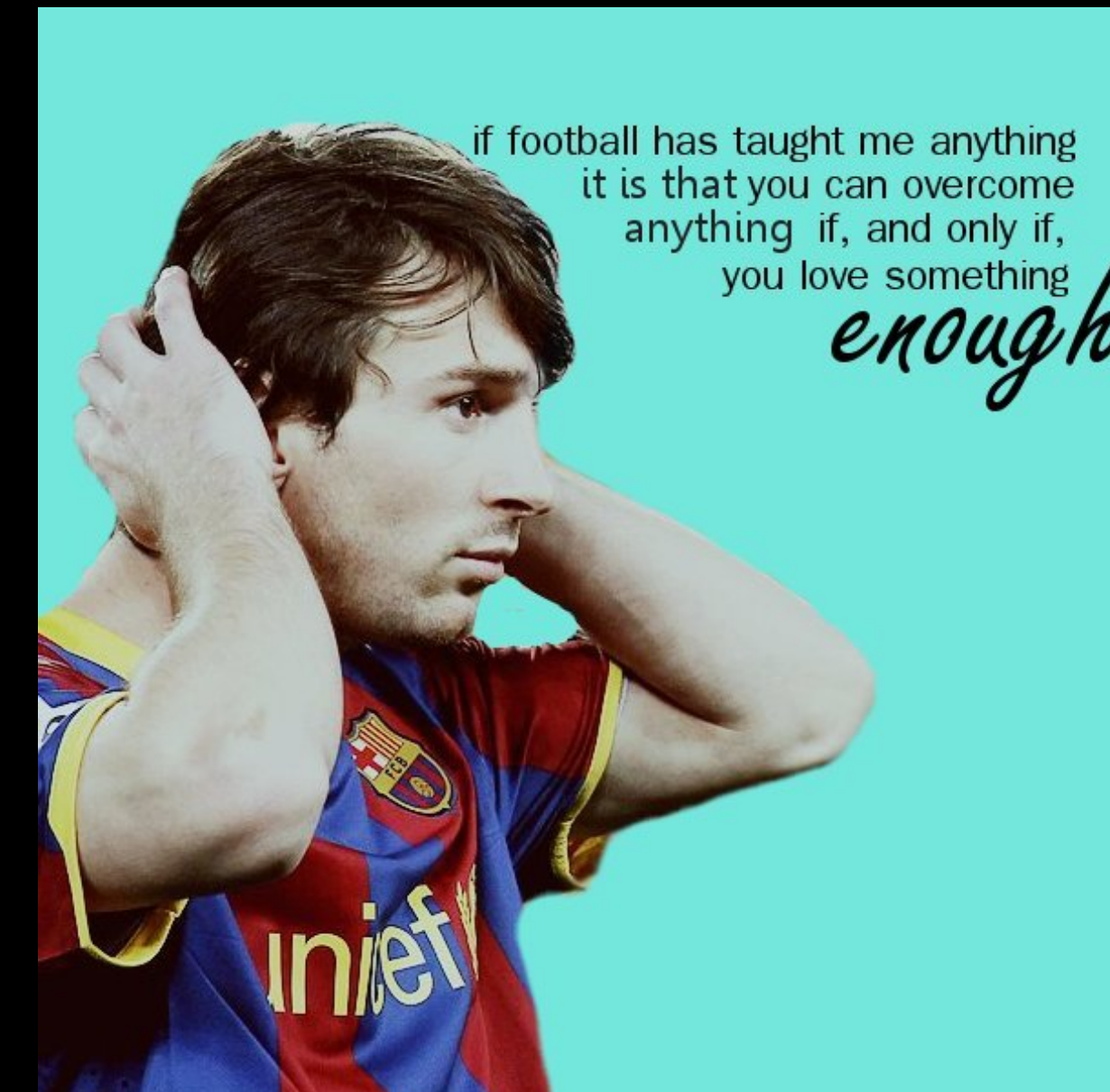
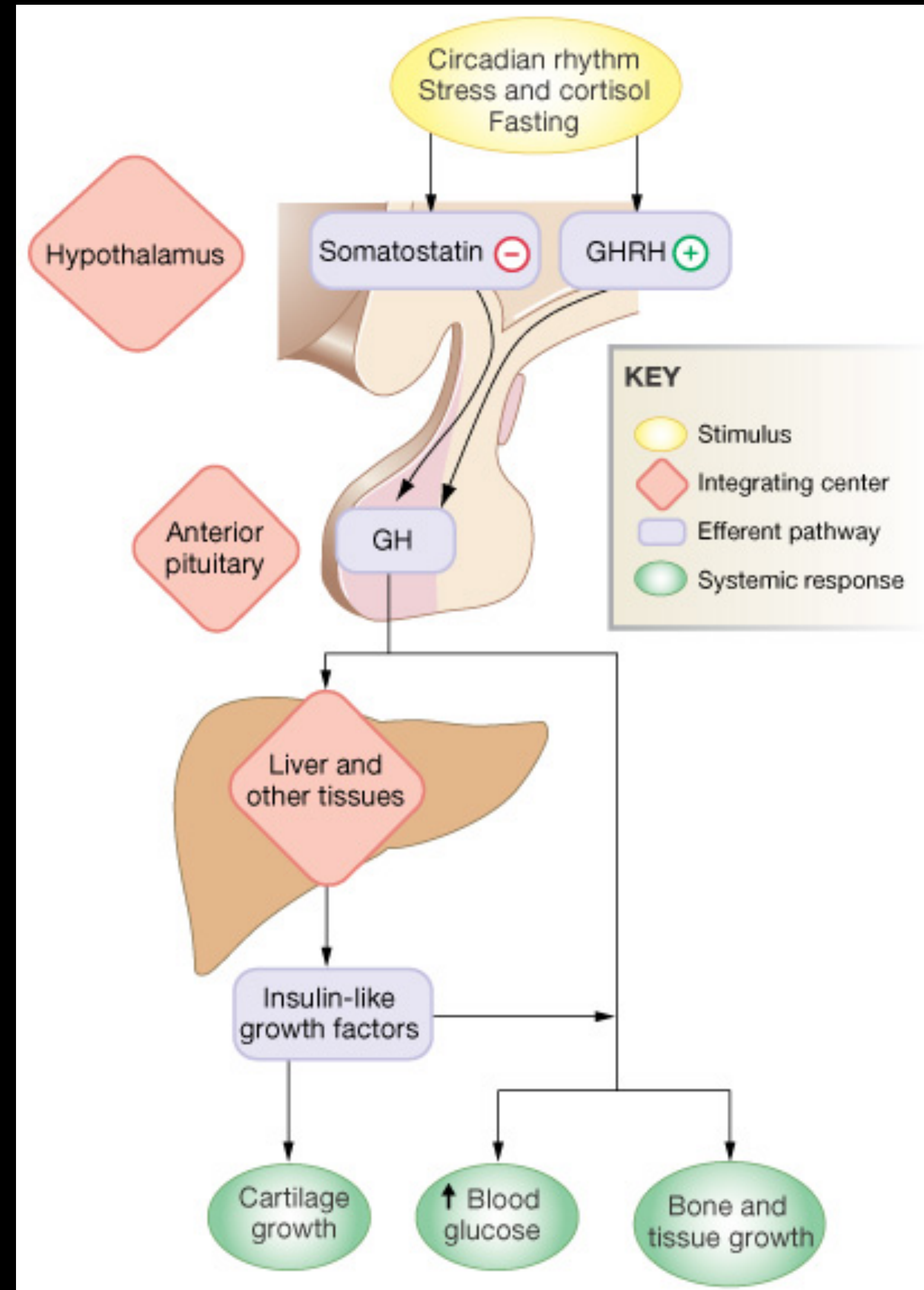
# Hypothalamus Pituitary axes



## PITUITARY GLAND



# Growth Hormone (GH): Functions & Malfunctions

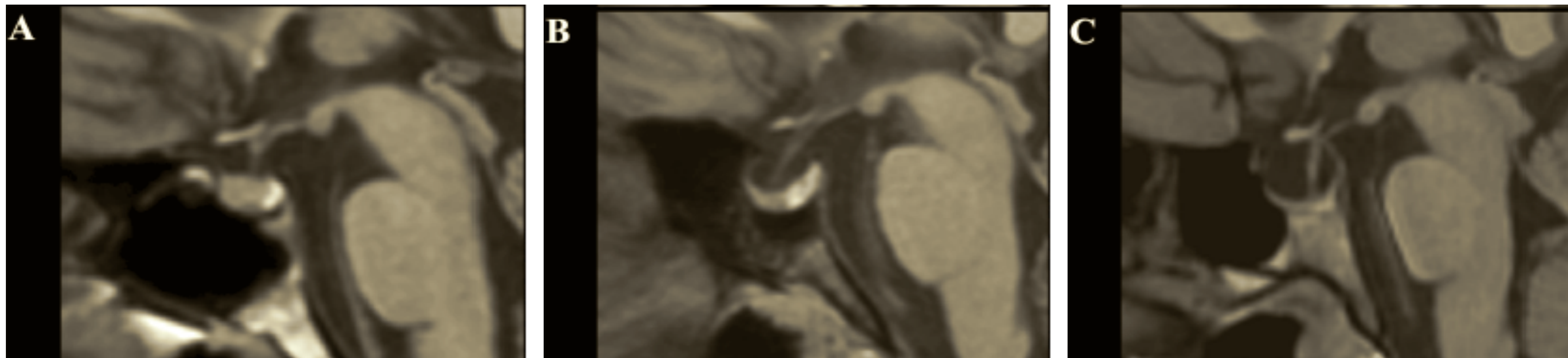


# PITUITARY MORPHOVOLUMETRIC CHANGES IN ALSTRÖM SYNDROME

Controls (21 subjects): partial empty sella 14%

Alstrom: 32 patients

**Normal 47%    Partial empty 19%    Total empty 34%**



# How do we assess growth ?

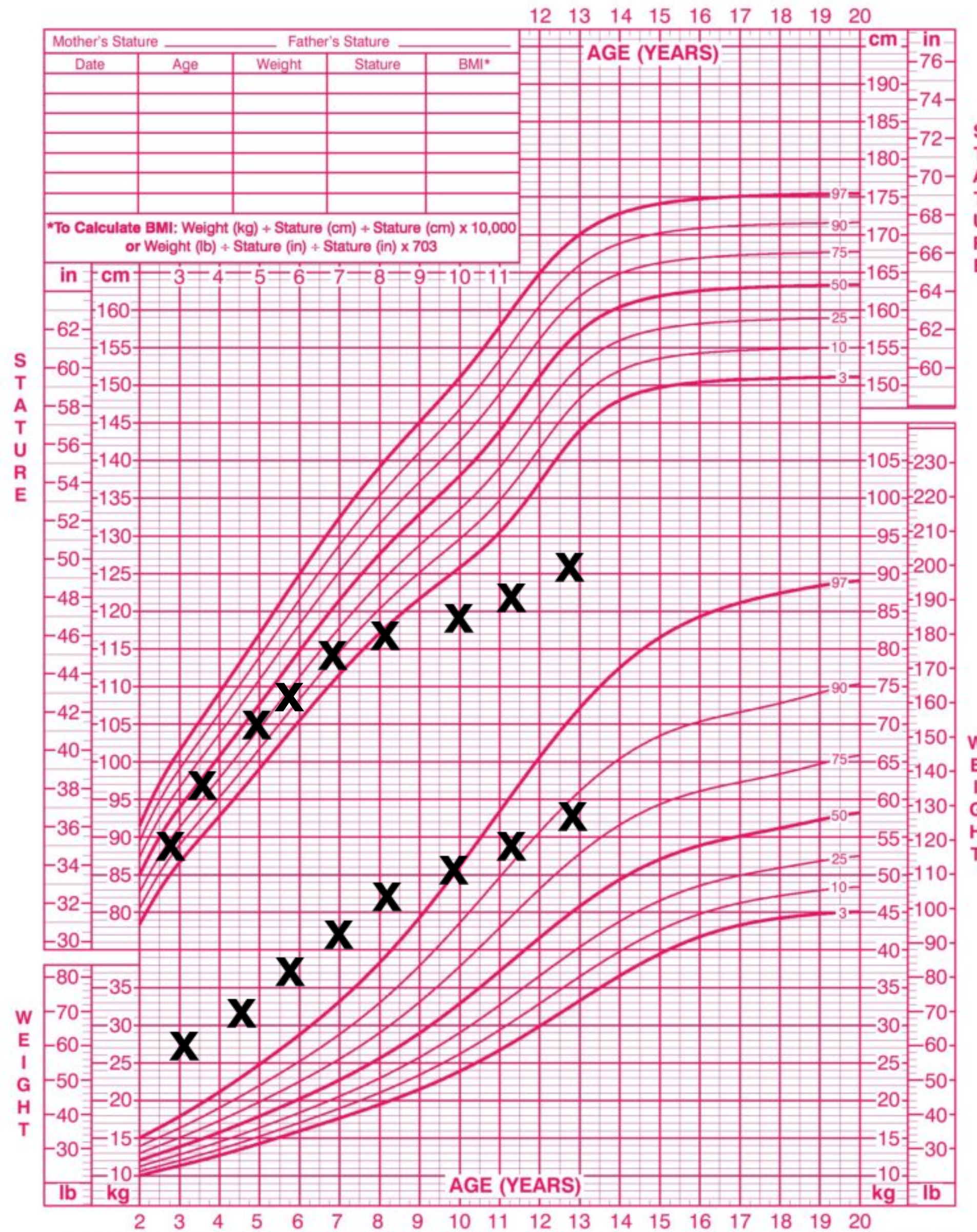
- Clinical examination
- Growth charts (repeated measurements)
- Bone age (hand X-ray)
- Laboratory:
  - liver, kidney function...
  - thyroid, gonadal function...
  - basal and stimulated GH
  - IGF-I
- Pituitary MRI



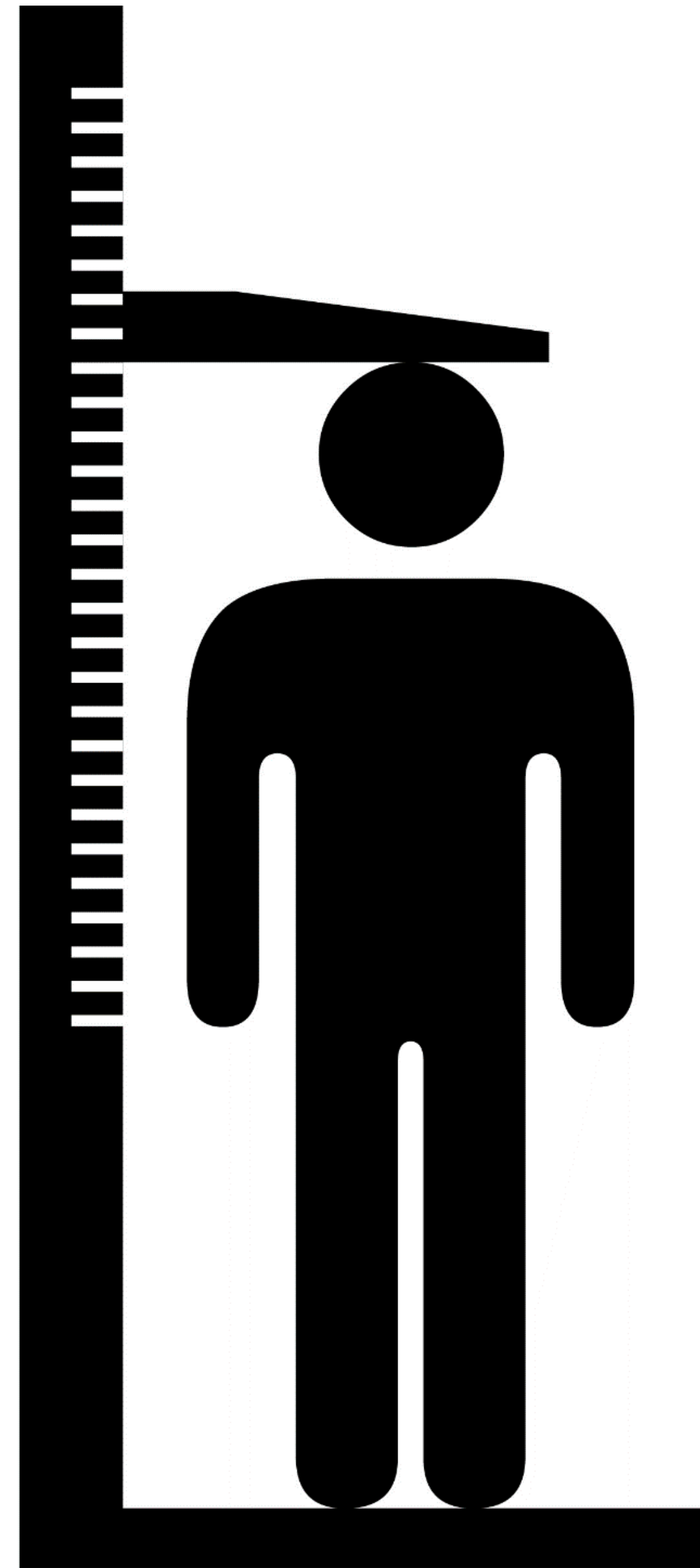
**2 to 20 years: Girls**  
**Stature-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_



Published May 30, 2000 (modified 11/21/00).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with  
 the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>



# Symptoms of adult GHD

- Increased weight and body fat mass
- Reduced muscle bulk
- Reduced strength and physical fitness
- Reduced sweating
- Reduced vitality
- Impaired psychological well-being
- Poor sleep



# Signs of adult GHD

- Overweight
- Increased adiposity, especially abdominal
- Poor muscular development
- Reduced exercise performance
- Thin, dry skin
- Depressed affect
- Reduced cardiac performance
- Reduced bone density and increased fracture rate

# Outcomes-based criteria for treatment of AGHD

- 6-12 months trial of GH therapy
- start with 0.15-0.3 mg/daily s.c.
  - (GHRH - individualized dose)
- dose titration to a mid-range normal IGF-I level
- objective measures of improvement
  - DEXA scanning for BMD
    - DEXA scanning for body composition
    - serum lipids
    - exercise duration and amount
    - QOL questionnaires

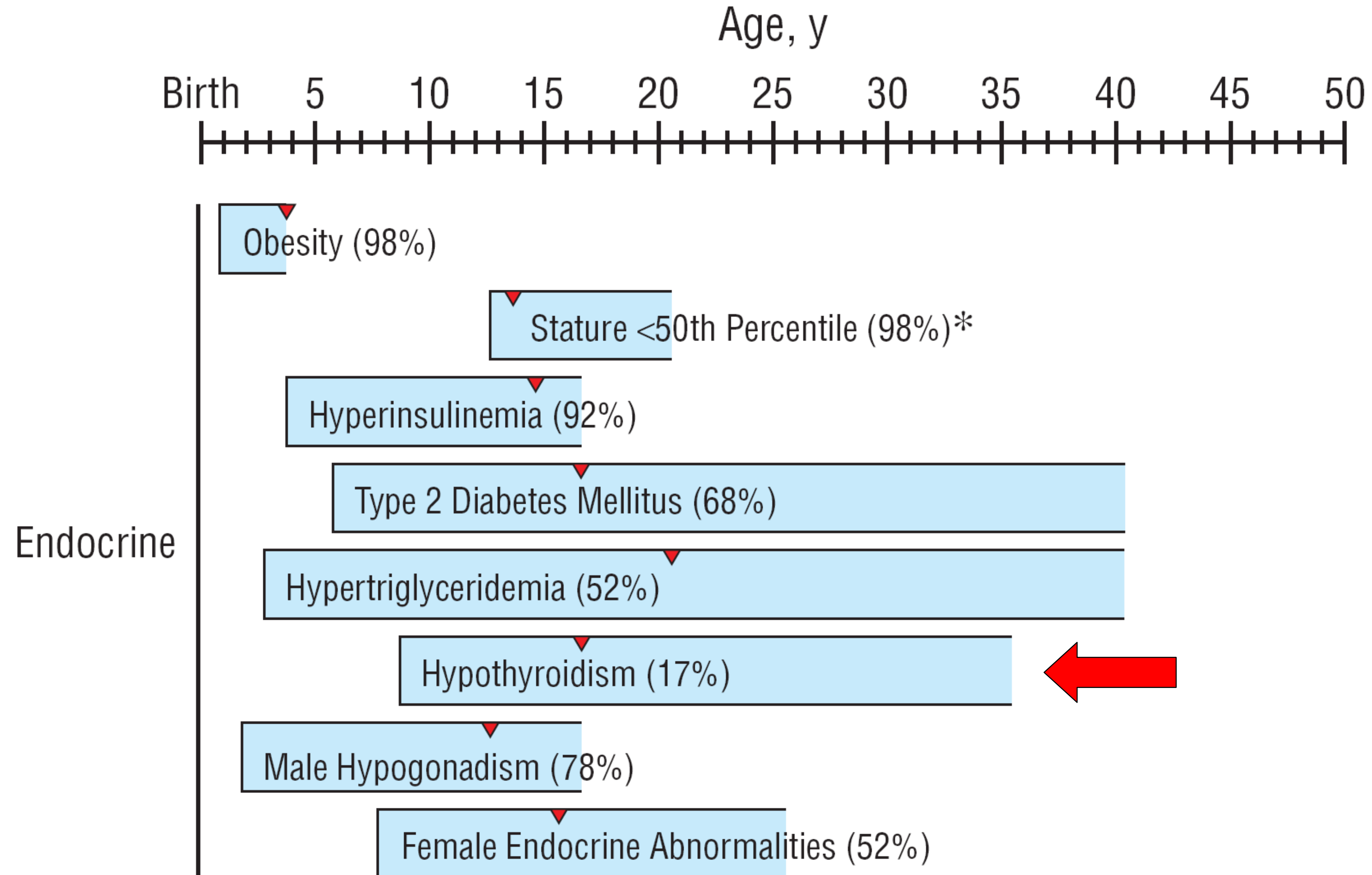


# Side Effects of rGH Treatment

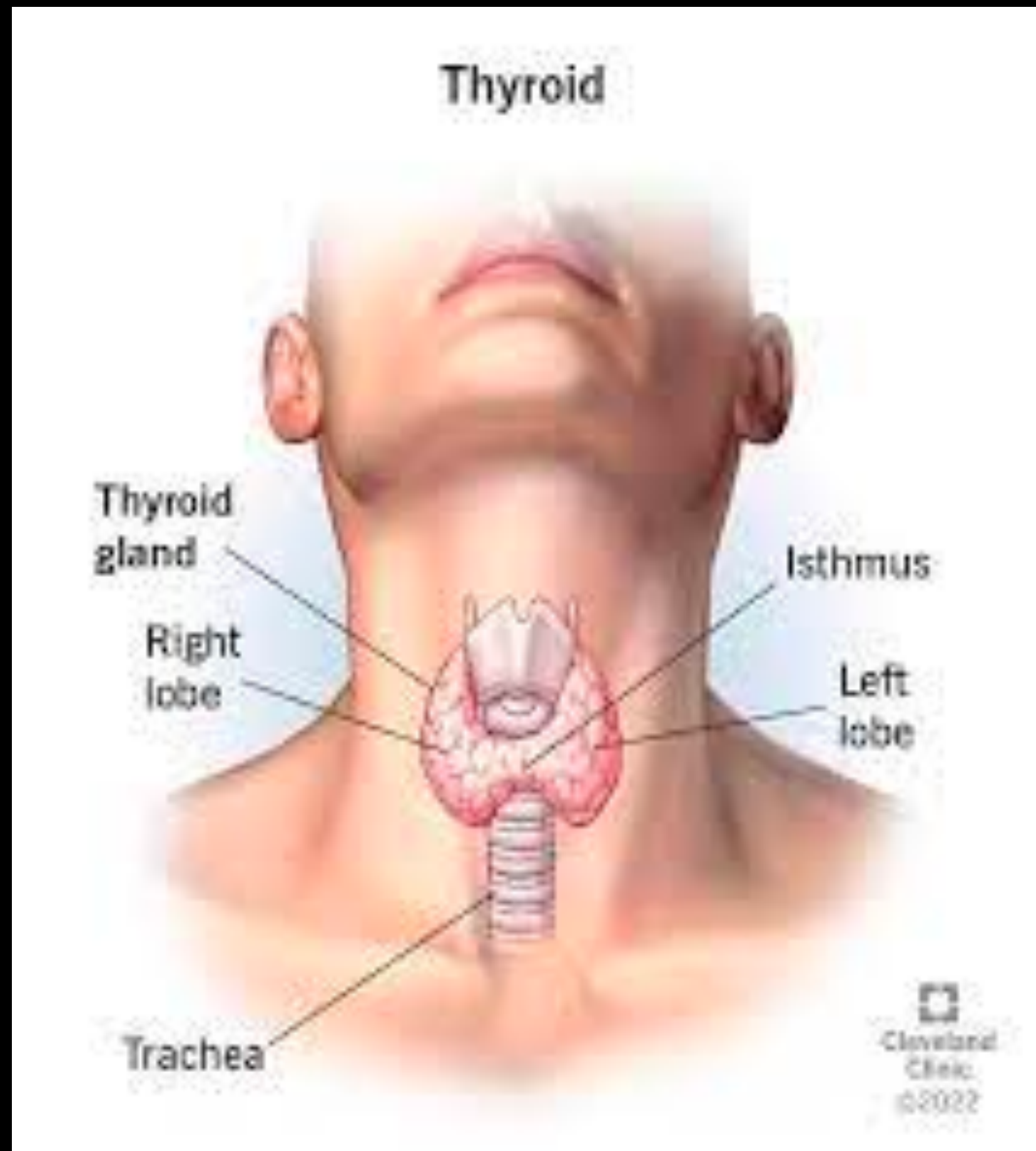
- Fluid retention, edema (37.4 %)
- Arthralgia (19.1 %)
- Myalgia (15.7 %)
- Paresthesias (7.8 %)
- Carpal Tunnel Syndrome (1.7 %)
- Pseudotumor cerebri/benign intracranial hypert...
- Slipped capital femoral epiphysis
- Lipoatrophy (injection sites)
- Transient resistance to the action of insulin
- Pancreatitis
- Transient gynecomastia



# Phenotype – 182 patients



# Thyroid gland abnormalities



Salt iodized



↑ growth  
↑ metabolism  
Thermogenic

# Symptoms of hypothyroidism

|                    |     |                       |     |
|--------------------|-----|-----------------------|-----|
| Weakness           | 99% | Constipation          | 61% |
| Dry skin           | 97% | Gain in weight        | 59% |
| Coarse skin        | 97% | Loss of hair          | 57% |
| Lethargy           | 91% | Pallor of lips        | 57% |
| Slow speech        | 91% | Dyspnea               | 55% |
| Edema of eyelids   | 90% | Peripheral edema      | 55% |
| Sensation of cold  | 89% | Hoarseness or aphonia | 52% |
| Decreased sweating | 89% | Anorexia              | 45% |
| Cold skin          | 83% | Nervousness           | 35% |
| Thick tongue       | 82% | Menorrhagia           | 32% |
| Edema of face      | 79% | Palpitation           | 31% |
| Coarseness of hair | 76% | Deafness              | 30% |
| Pallor of skin     | 67% | Precordial pain       | 25% |
| Memory impairment  | 66% |                       |     |

# How do we Study the Thyroid Gland ?

- **Clinical Examination**
  - goiter, nodules...
- **Laboratory:**
  - FT4 and TSH
  - Autoantibodies
- **Imaging:**
  - US
  - Scintigraphy



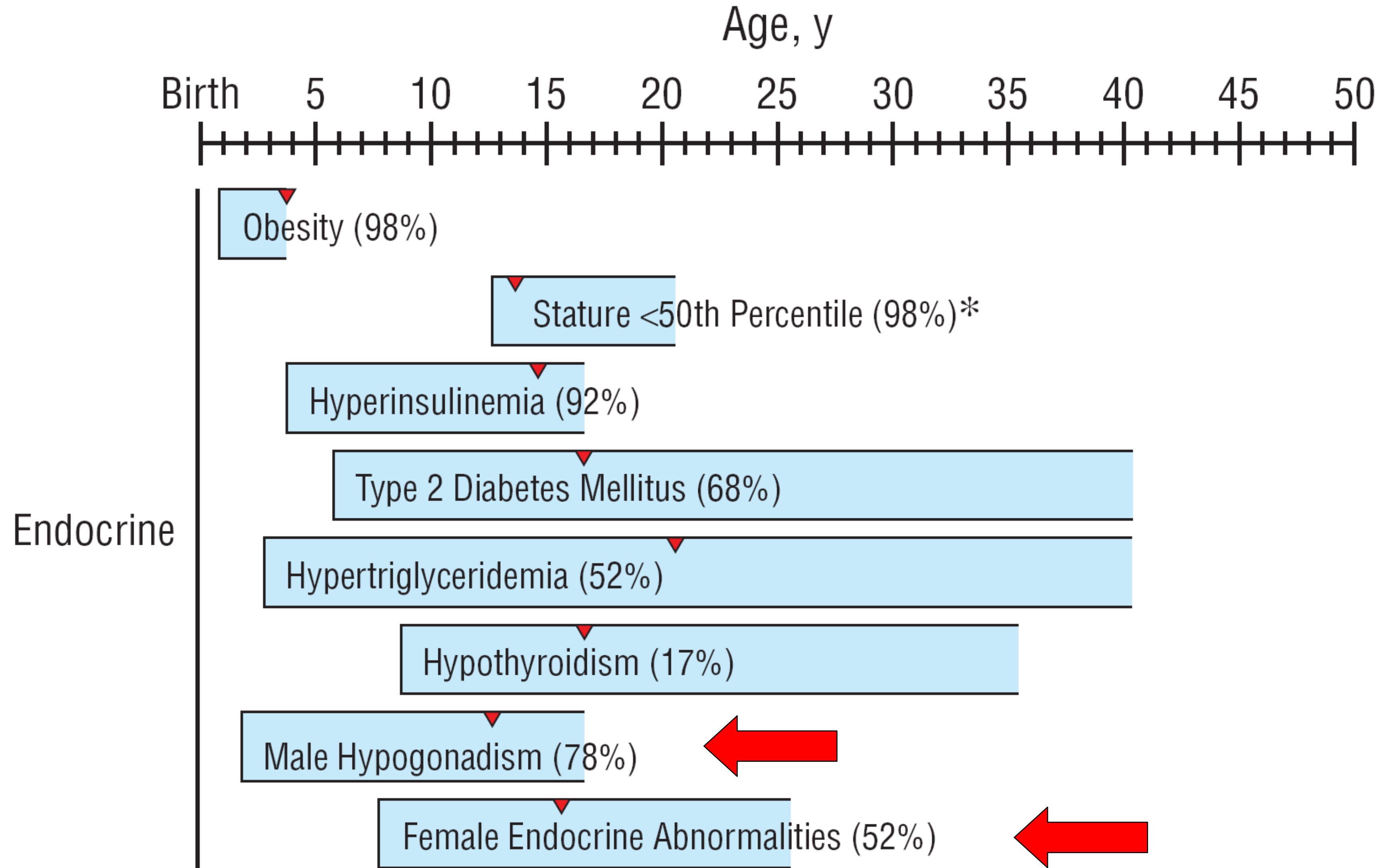
# Therapy of Hypothyroidism

- **L-thyroxin**
  - 25-200 mcg once daily in the morning
  - fasting !
- **L-thyroxin half-life**
  - 7 days
- **TSH < 4**
  - annual basis control
- **start with low dosages**
  - 25 mcg
- **excessive doses**
  - osteoporosis
  - atrial fibrillation

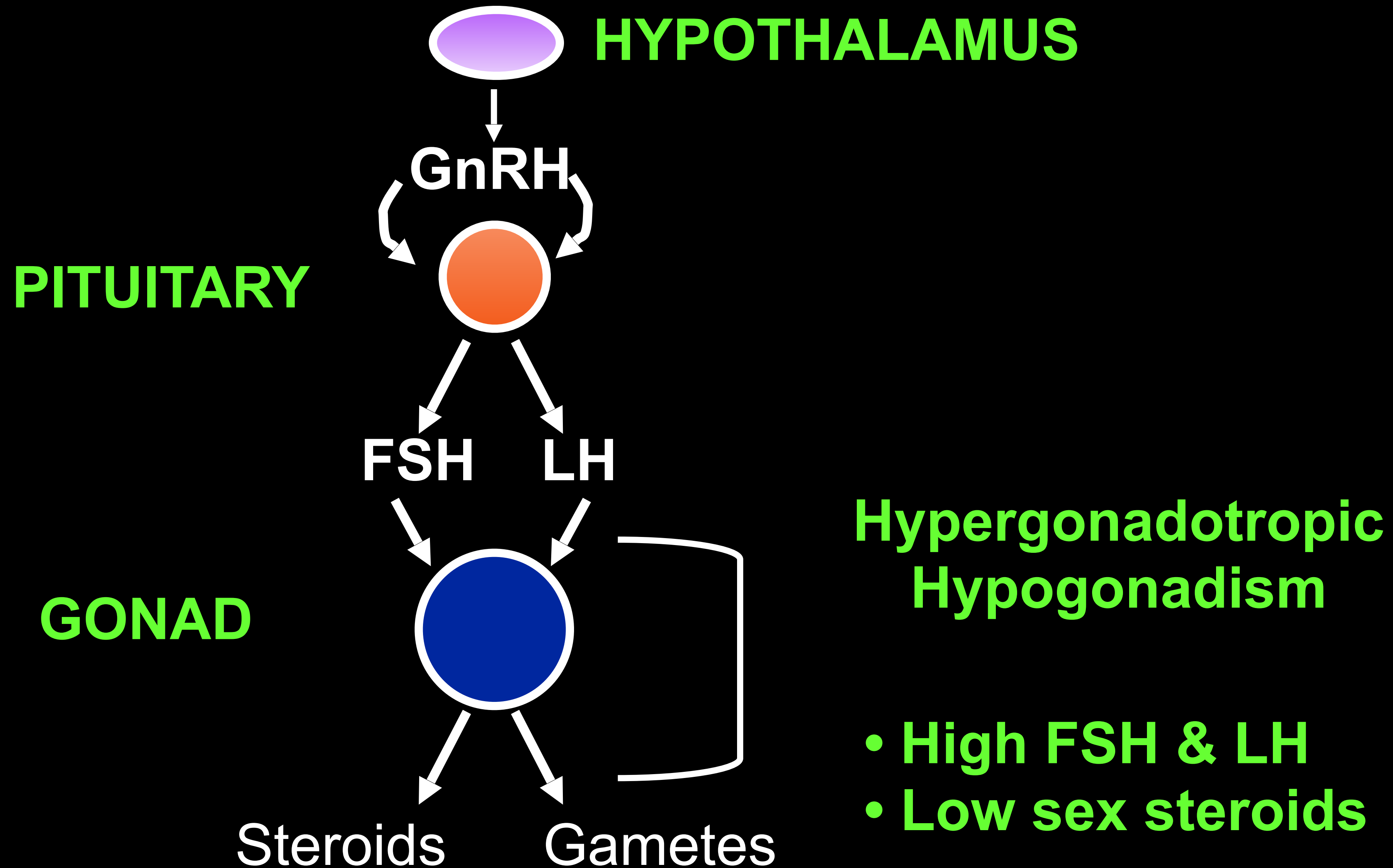




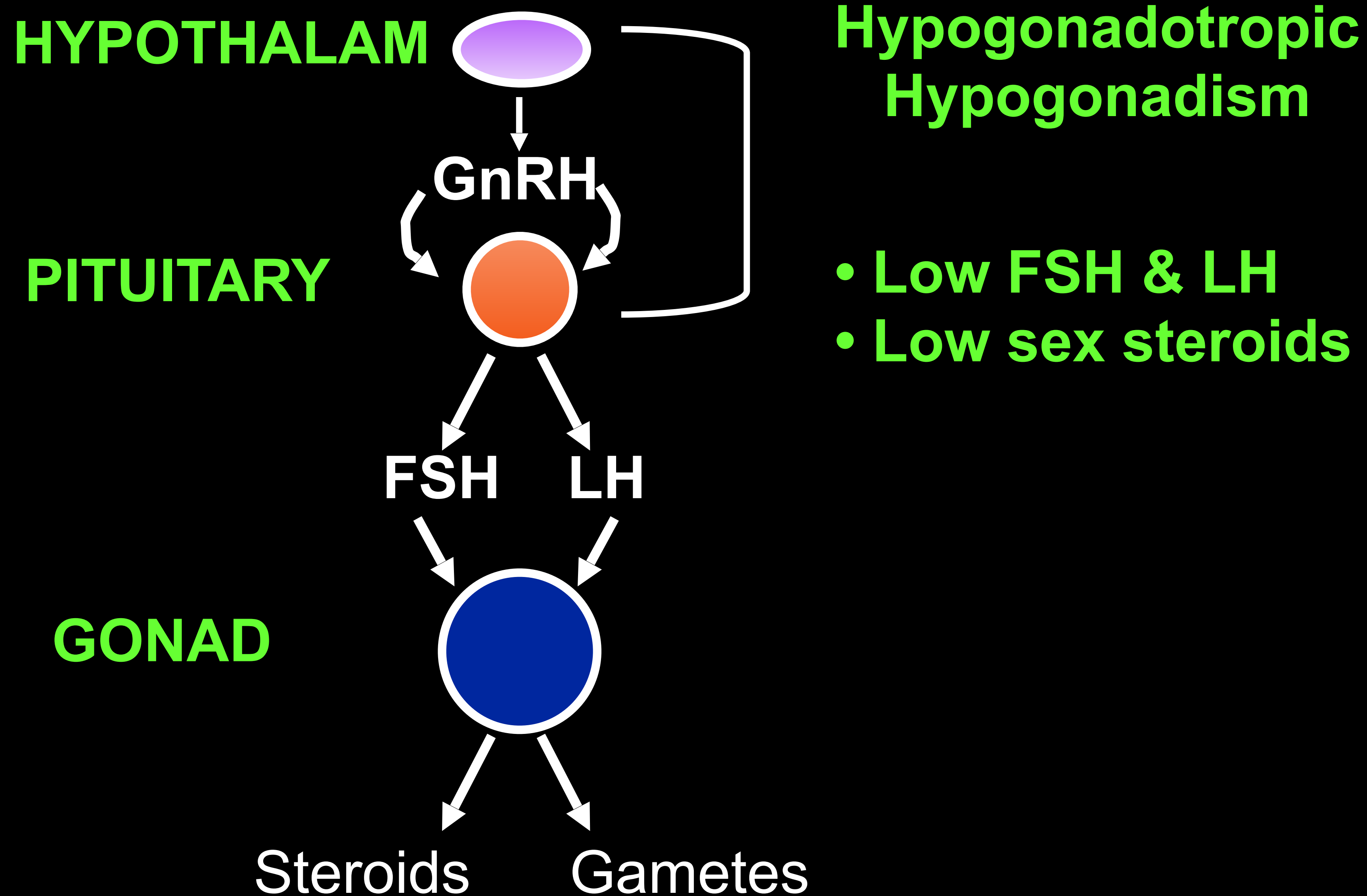
# Phenotype – 182 patients



# H-P-G Axis Dysfunction



# H-P-G Axis Dysfunction



# Normal Pubertal Milestones

## Females

**Breasts: age 9-11**

**Pubic hair: 8-9**

**Growth spurt: 12**

**Menses: age 12**

## Males




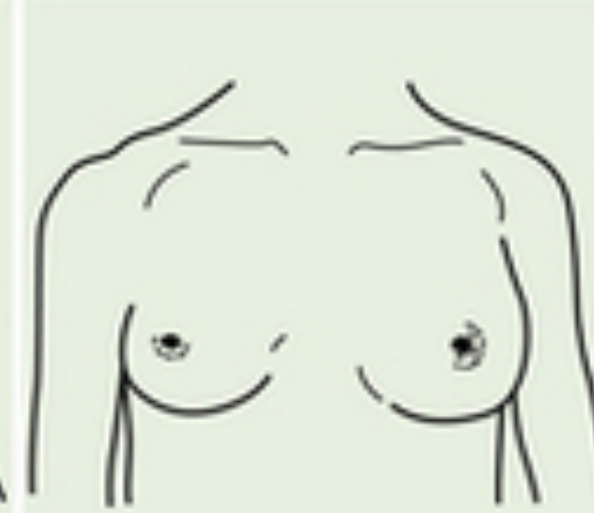
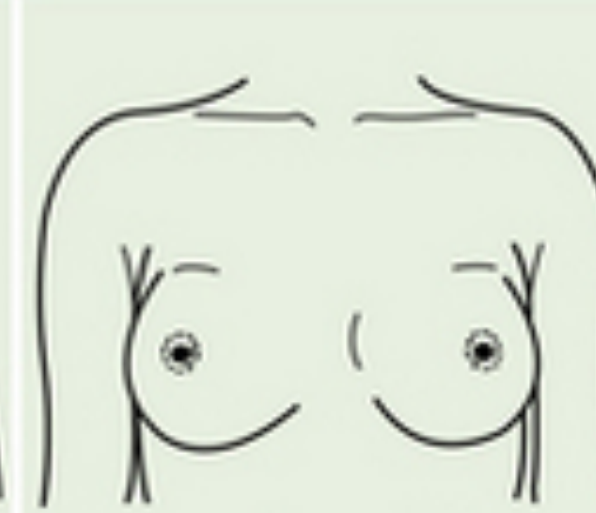





**Testes: age 10-11**

**Pubic hair: 10-11**

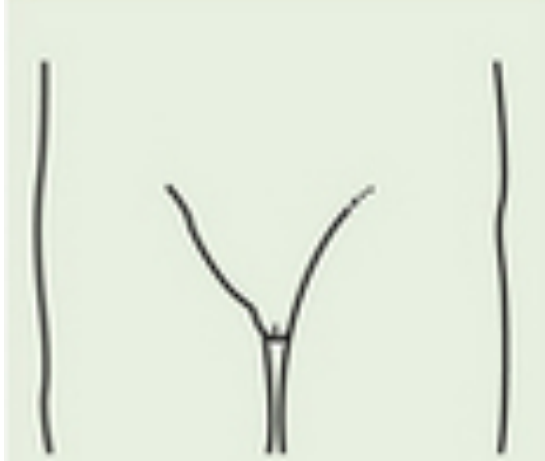



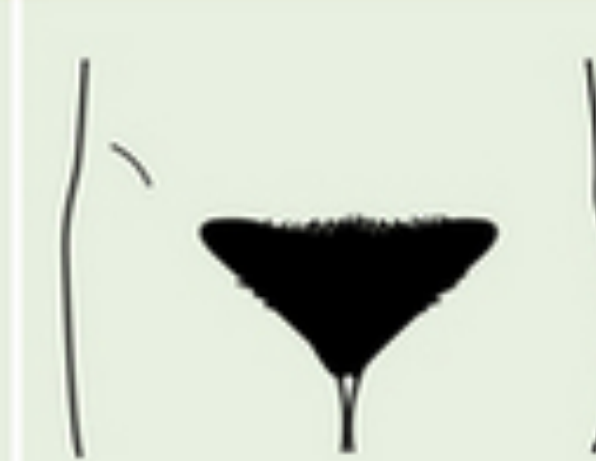
**Penile growth: 13**

**Growth spurt: 14**

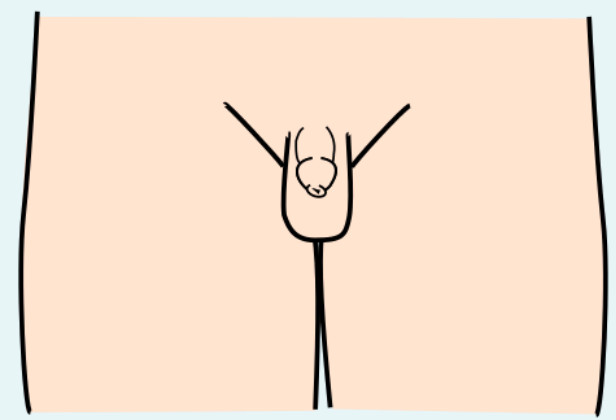
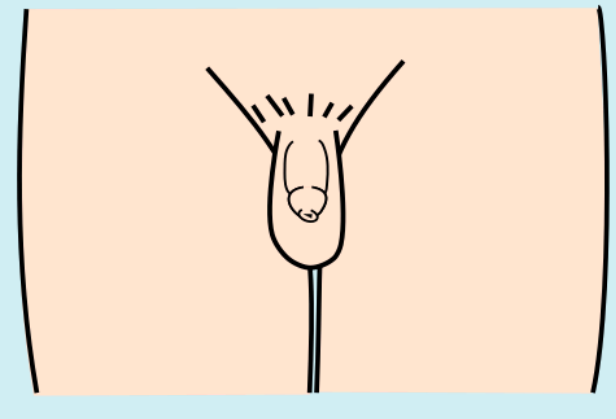
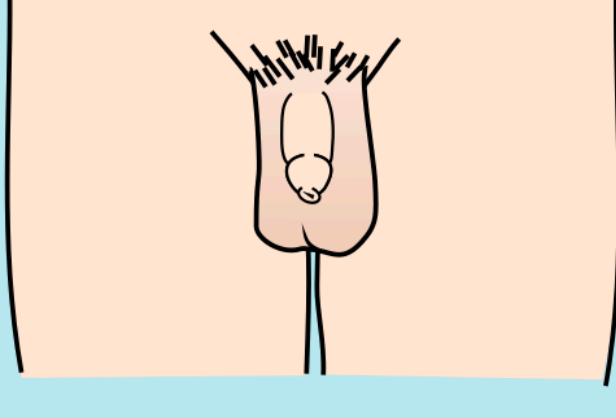


# Tanner's Table (female)

| Stages of female breast development  |   |  |  |   |
|--|---|--|--|---|
|  |  |  |             |        |
|  |  |  |             |        |
| 1 Prepubertal, elevation of papilla only   | 2 Breast buds are noted or palpable, enlargement of the areola                    | 3 Further enlargement of the breast and areola with no separation of the contours  | 4 Projection of the areola and papilla to form a secondary mound above the level of the breast | 5 Adult contour breast with projection of papilla only, areola recesses to breast contour |

| Stages of pubic hair development   |   |  |   |   |
|--|---|--|---|---|
|  |  |  |  |  |
| 1 Prepubertal, no pubic hair   | 2 Sparse growth of minimally pigmented hair, mainly on the labia                    | 3 Considerably darker and coarser hair spreading over the mons pubis                 | 4 Thick adult-type hair that does not yet spread to the medial surface of the thighs  | 5 Adult-type hair distributed on classical inverse triangle                           |

# Tanner's Table (male)

|     |   |    |         |
|-----|---|----|---------|
| I   |    | 3  | <2,5    |
| II  |    | 4  | 2,5-3,2 |
| III |   | 10 | 3,6     |
| IV  |  | 16 | 4,1-4,5 |
| V   |  | 25 | >4,5    |

# Symptoms and Signs of Male Hypogonadism

## (prior to puberty)

- Linear growth may continue after age 18 if untreated
- Disproportionately long arms and legs
- Scant pubic and axillary hair
- Infantile genitalia and prostate
- Lack of scrotal pigmentation and rugae
- High pitched voice
- Decreased libido
- Decreased muscle mass and strength
- Diminished endurance
- Gynecomastia

# Symptoms and Signs of Male Hypogonadism (post-pubertal)

- Loss of libido
- Hot flushes
- Erectile dysfunction
- Fatigue
- Enlarged breasts
- Problems sleeping
- Loss of body hair
- Lethargy
- Loss of muscle mass and muscle strength
- Oligospermia and azoospermia (infertility)
- Reduction of bone density
- Regression of secondary sexual characteristics
- Depression, mood changes, difficulty concentrating

# Diagnosis

- History and Physical examination
  - Tanner's Tables
- Laboratory studies
  - testosterone, 17-beta-estradiol, progesterone
  - gonadotropins (FSH, LH)
  - stimulation tests (GnRH, Clomiphene, hCG)
  - PRL
  - semen analysis
- Other studies
  - bone densitometry
  - pituitary MRI
  - genetic studies
  - testicular biopsy
  - testicular or pelvic US



# Goals of therapy

- Restore sexual function, libido, well-being, behaviour
- Produce and maintain virilization
- Optimize bone density and prevent osteoporosis
- Possibly normalize GH levels
- Possibly reduce the potential risk of CV diseases
- Restore fertility

| What does testosterone do? |   |
|----------------------------|---|
| <b>Brain</b>               | Affects sex drive, mood, and mental processes (cognition)                     |
| <b>Skin</b>                | Affects male pattern body and facial hair, balding, and oil production        |
| <b>Larynx</b>              | Deepens voice and prompts formation of Adam's apple                           |
| <b>Organ</b>               | Stimulates production of erythropoietin, which causes red blood cells to form |
| <b>Male sexual organs</b>  | Affect penile and prostate growth and function and production of sperm        |
| <b>Muscle</b>              | Increases strength and muscle mass  |
| <b>Liver</b>               | Affects production of proteins  |
| <b>Fat</b>                 | Decreases fat mass  |
| <b>Bone marrow</b>         | Stimulates production of stem cells   |
| <b>Bone</b>                | Accelerates growth, increases bone strength, and maintains bone density       |

# Advantages and Disadvantages of Various Testosterone Deliveries

- **Injectables** - Inexpensive, every 2-4 wks, but “roller coaster” pharmacokinetics
- **Patches** - Mimics circadian rhythm, daily administration, but moderate pricing, skin irritation
- **Gels** - Generally good levels, daily administration, same transference, expensive
- **Oral** - liver toxicity, multiple dosing for lymphatic adsorption

# Possible Risks of Testosterone Replacement Therapy

- Acne
- Increased hematocrit (heart problems)
- Stimulation of occult adenocarcinoma of the prostate
- Worsening of symptoms of prostatism
- Decline in HDL
- Sleep apnea
- Psychosocial issues



# Menstrual Dysfunction

- **Oligo or amenorrhea**
  - Menstrual irregularity typically begins in the peripubertal period
  - Delayed menarche
- **Reduction in ovulatory events leads to deficient progesterone secretion**
- **Chronic estrogen stimulation of the endometrium with no progesterone for differentiation—intermittent breakthrough bleeding or dysfunctional uterine bleeding**
- **Increased risk for endometrial hyperplasia and/or endometrial CA**

# Clinical Features of Severe Insulin Resistance

- All subtypes

Acanthosis nigricans

Hyperandrogenism

Polycystic Ovaries

Oligomenorrhoea

Insulin-resistant diabetes



- Some subtypes

Dyslipidemia (high triglyceride, low HDL)

Lipodystrophy/abnormal fat topography

Pseudoacromegaloid soft tissue overgrowth

Abnormal linear growth (either retarded or accelerated)

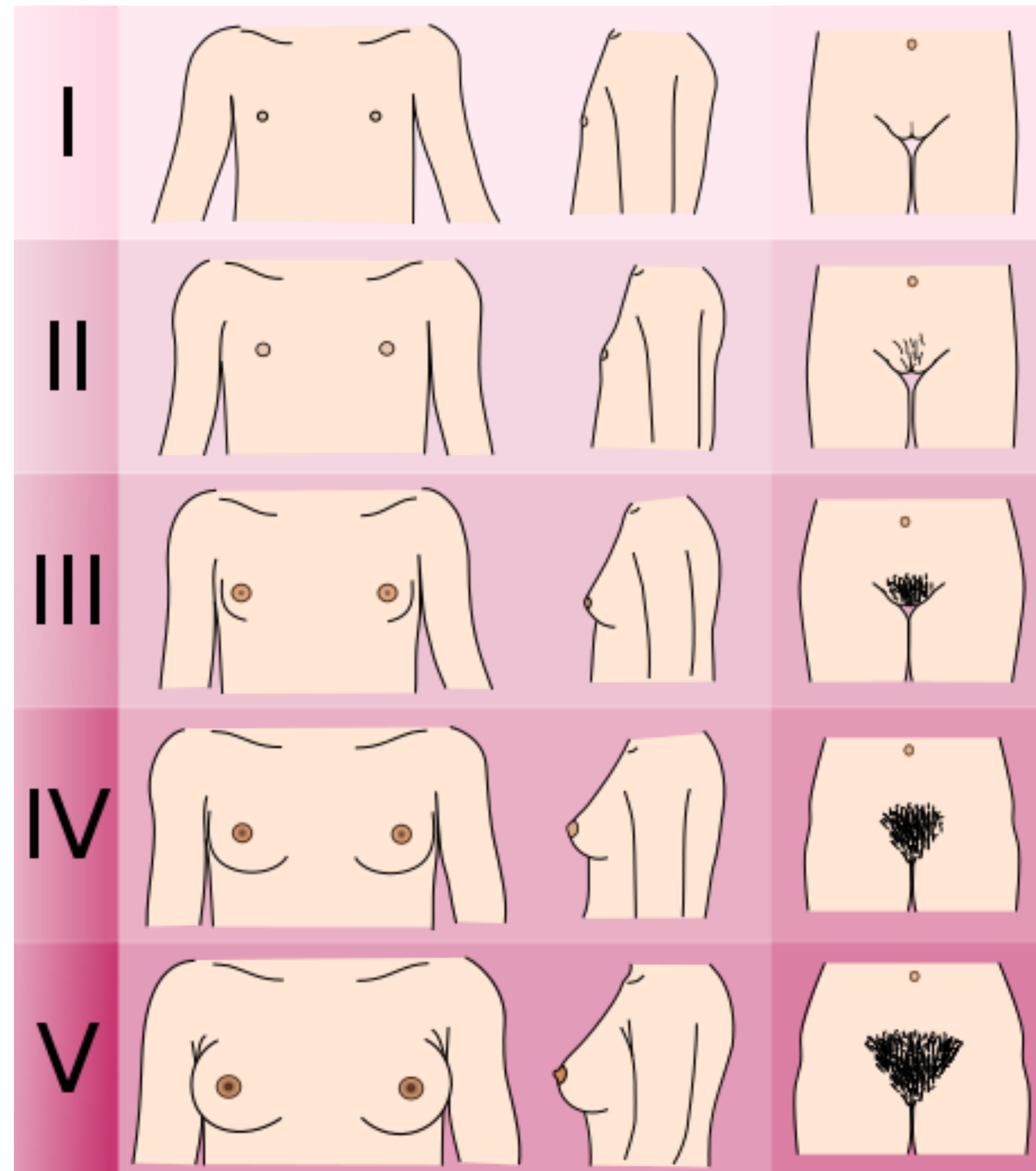
# Hyperandrogenism

- Hirsutism, acne, male pattern balding, alopecia
- 50-90% patients have elevated serum androgen levels
- Free testosterone levels most sensitive
- *Rare*: increased muscle mass, deepening voice, clitoromegaly (should prompt search for underlying neoplasm)

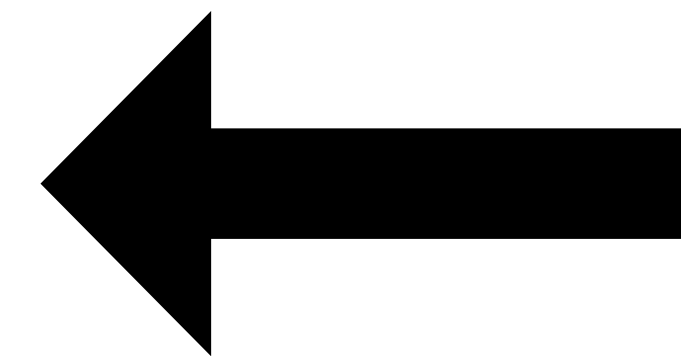
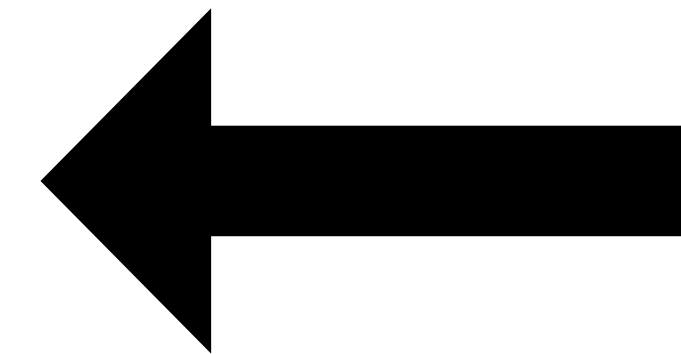
# Treatment of Oligomenorrhea

- Combination estrogen-progestin
- Monophasic antiandrogenic OCP
- Cyclic progestin
- Metformin

# Tanner scale for breast and pubic hair



**Common findings in AS**



**Present Case**





# Typical and mild gynecological phenotype of Alström syndrome

## Typical Phenotype

## Mild Phenotype

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Alopecia and hirsutism

Normal

Abnormal breast development

Normal

Ovary cysts

Normal

A/Oligomenorrhea

Normal

Hyperandrogenism

Mild increase in testosterone levels

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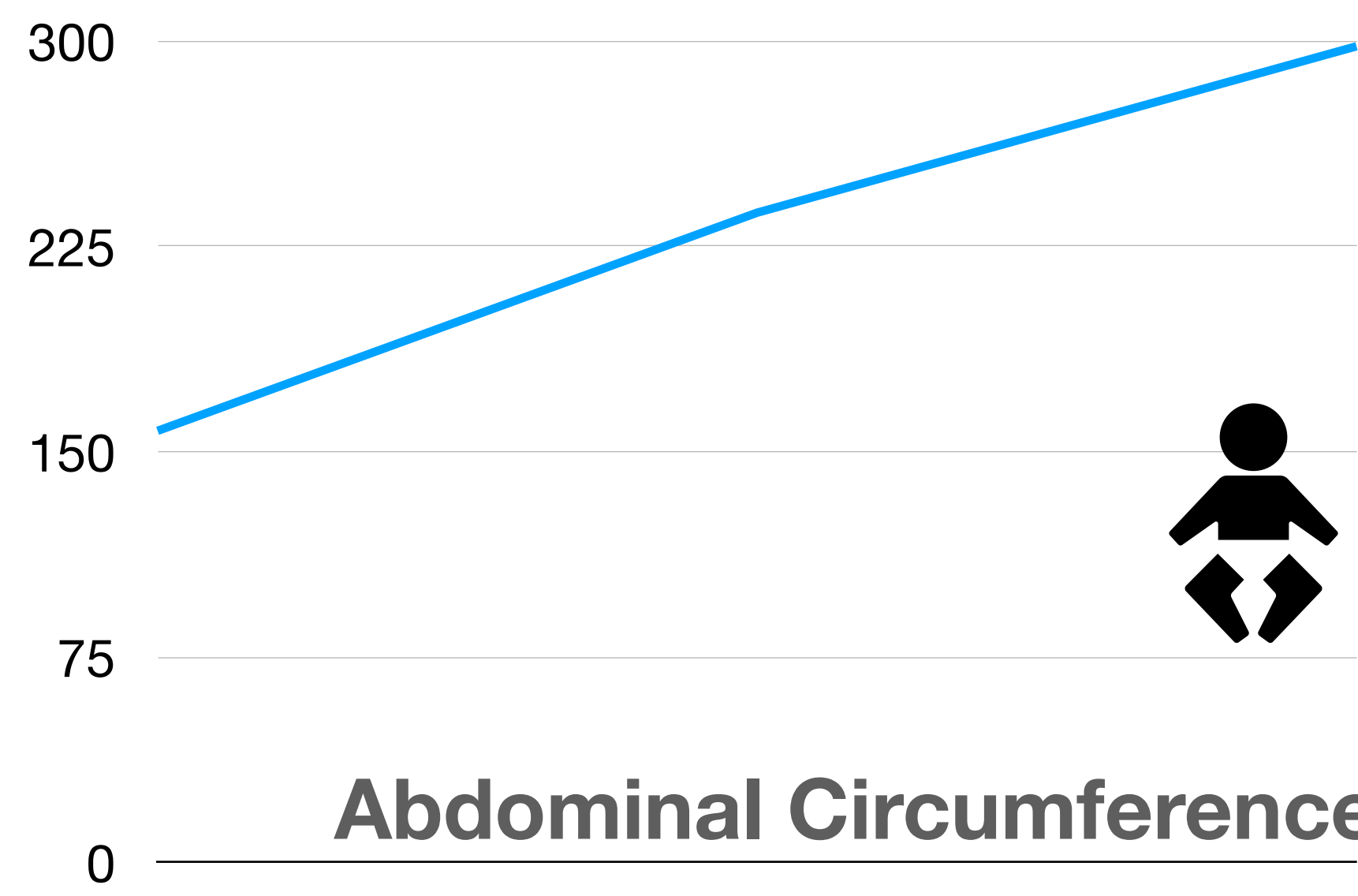
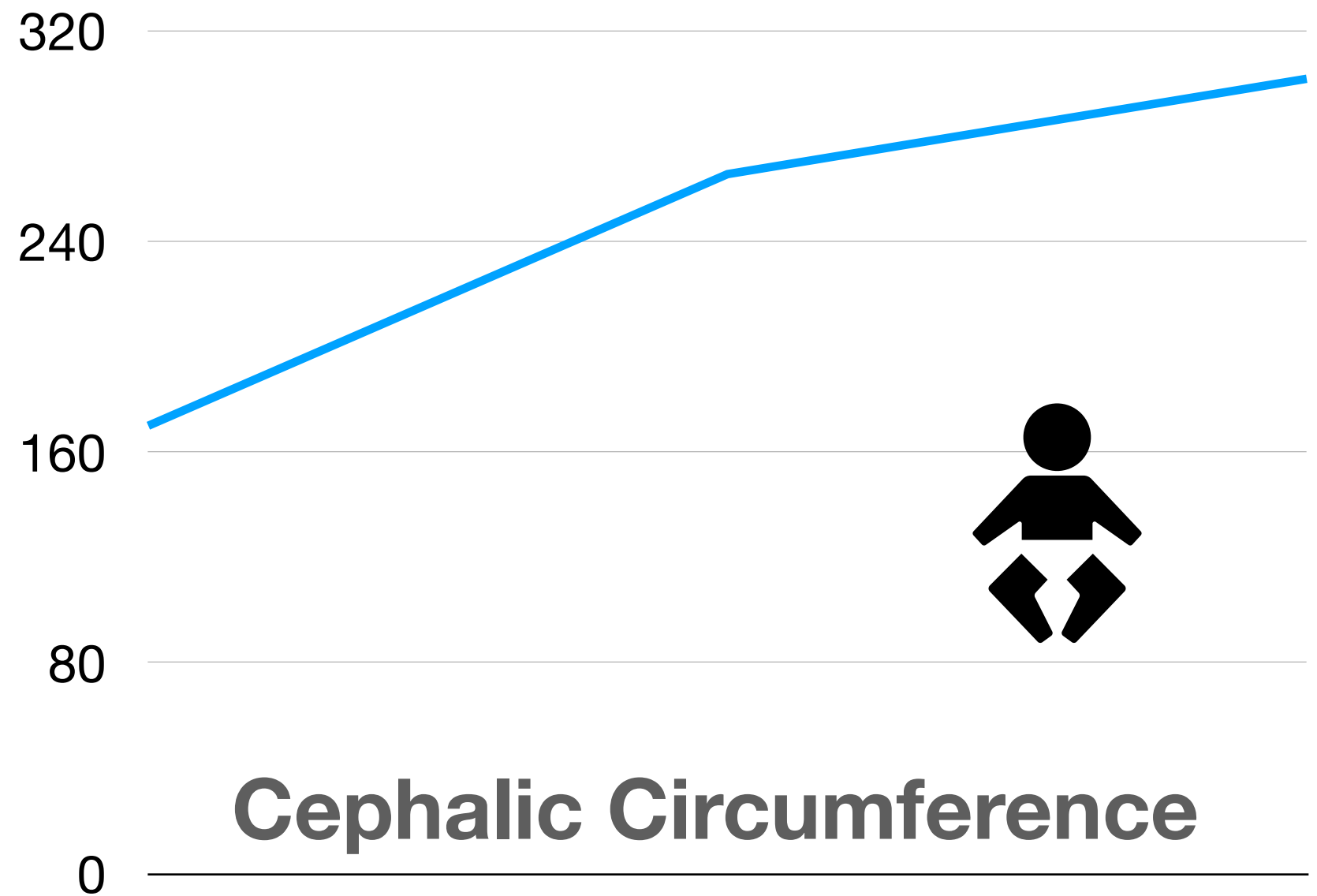
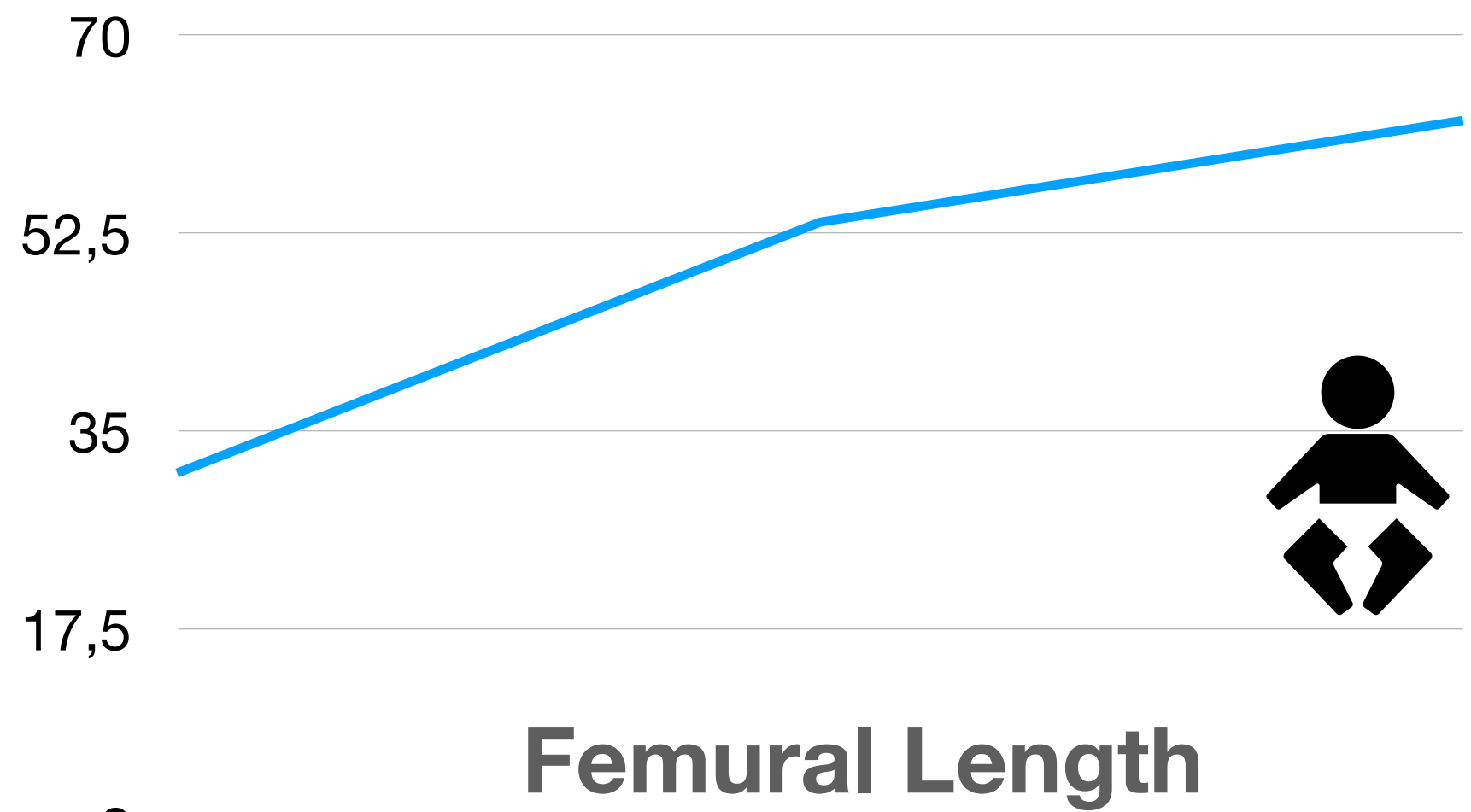
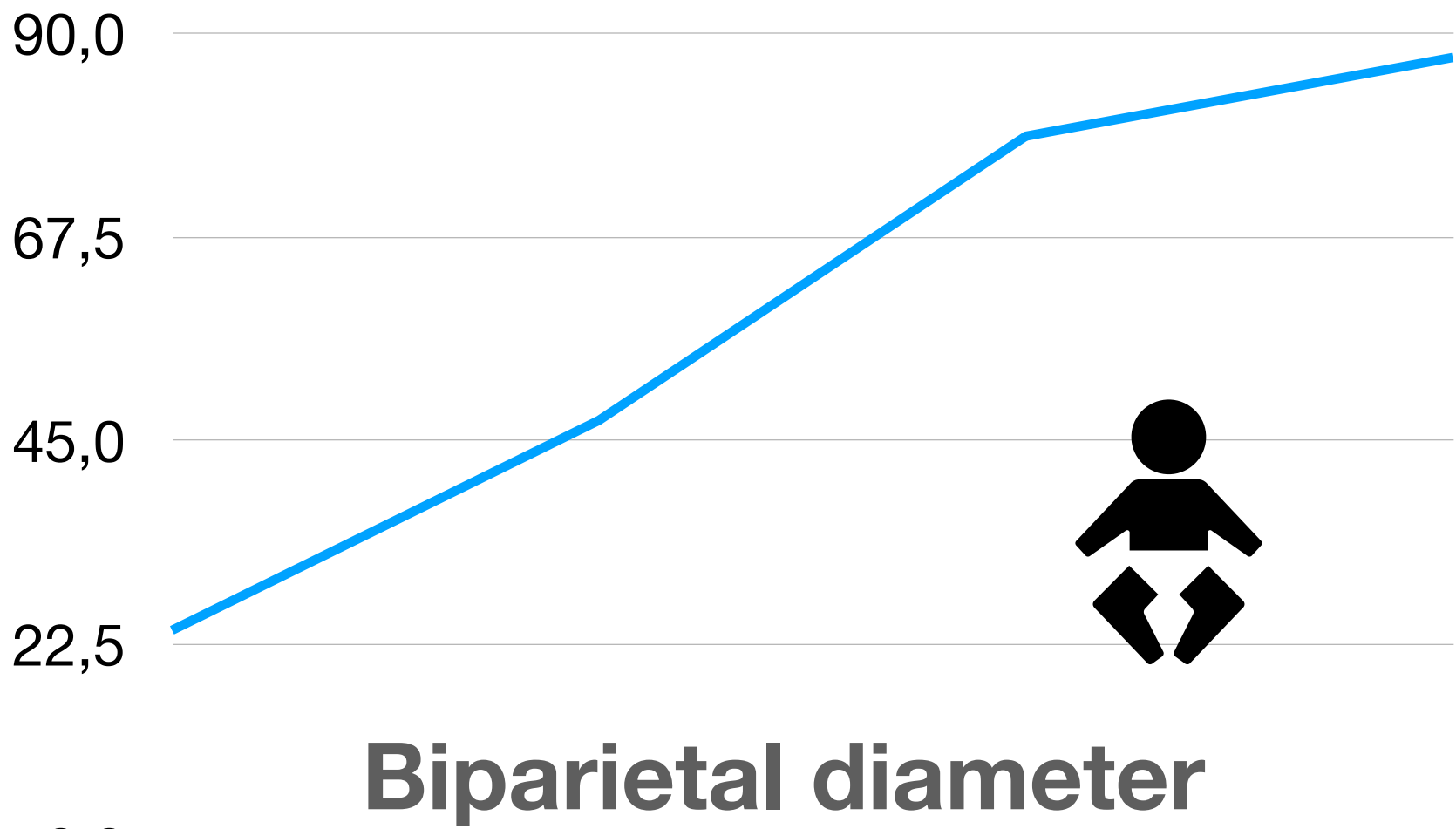
January 12, 2021



# Regular fetal growth



Sept 04, 2020 (10 wk +0)  
Sept 18, 2020 (12 wk+0)  
*Nov 10, 2020 (20 wk+4)*  
*Jan 12, 2021 (29 wk+4)*  
*Feb 14, 2021 (34 wk+2)*



# Other US results along the pregnancy



- **Heart activity:** regular
- **Fetal movement:** regular
- **Amniotic fluid volume:** normal
- **Fetal presentation:** cephalic
- **Placental position:** posterior
- **Biometric fetal growth:** regular (diameters or circumferences)
- **Doppler US of umbilical artery:** regular (pulsatility index 0.87)
- **Any malformation of:** head-brain-face, spine, heart, major vessels, lungs, abdominal wall, stomach, kidney, bladder, bones

# Course of Pregnancy and Delivery

- **13 wk-26 wk:** monthly screening, regular clinical and lab results
- **26 wk:** dipstick proteinuria (not confirmed at 24h urine test)
- **34 wk:** hypertension and peripheral edema, cholestasis
- **34 wk:** hospitalization
  - Therapy:
    - Corticosteroids for respiratory distress syndrome prophylaxis
    - nifedipine 20 mg → STOP (lack of efficacy)
    - alpha-methyldopa 500 mg + labetalol 100 mg
    - Ursodeoxycholic acid 450 mg



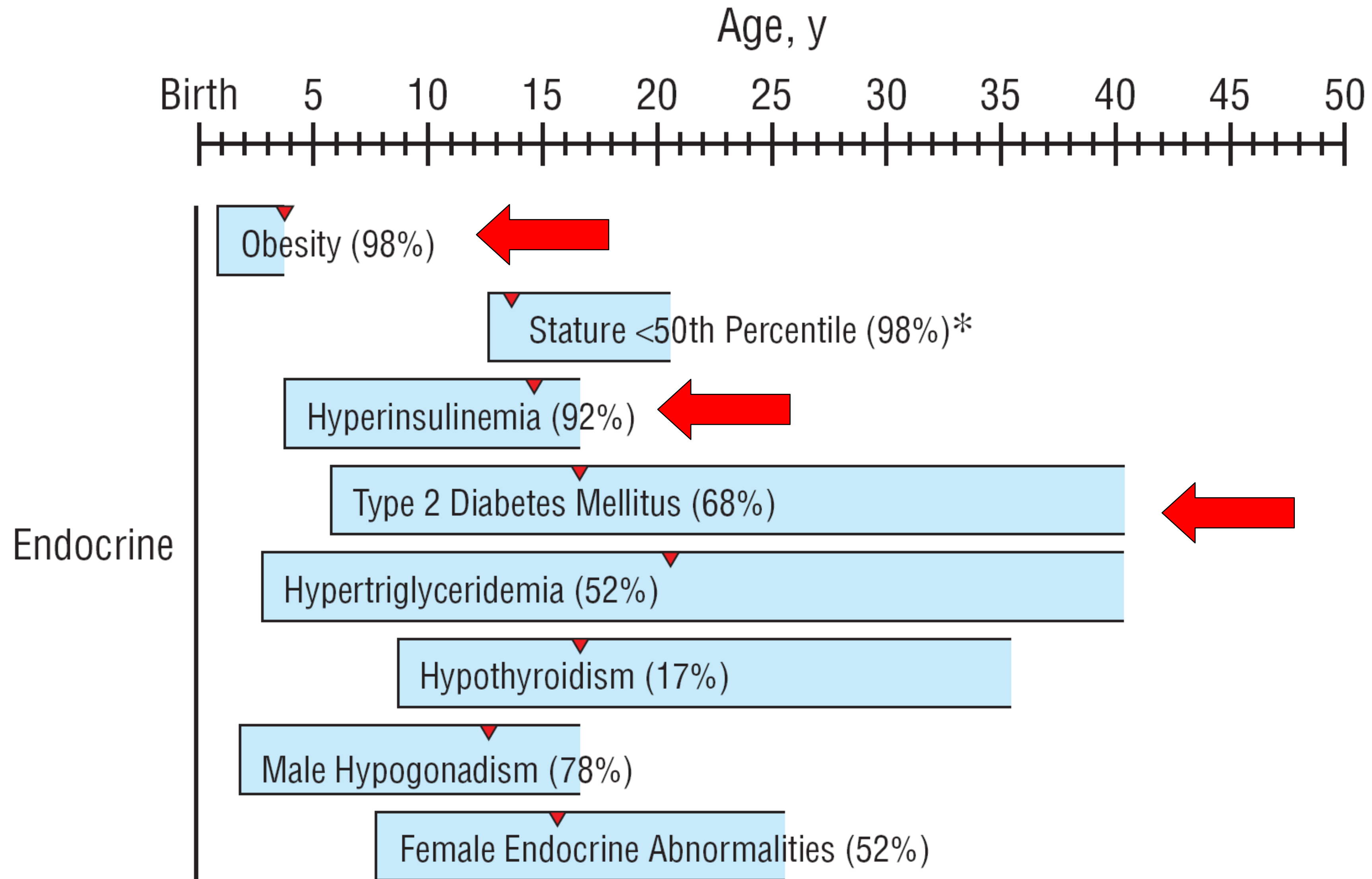


# Postnatal...

- Hospital discharge after 6 days
- No lactation after delivery
- Resumption of regular menstrual cycle
- Therapy: ramipril 5 mg
- Regular growth of the new-born



# Phenotype – 182 patients







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CHI SIAMO

LA SINDROME DI ALSTRÖM

LE NOSTRE ATTIVITA'

CONTATTI

ASSOCIARSI

CONVEGNO DELLE FAMIGLIE 2023

ASS.A.I. IN ENGLISH





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