Diseases of the gonads

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Definition

Hypogonadism is a medical term for decreased functional activity of the gonads.

The gonads (ovaries or testes) produce

☑hormones

testosterone, estradiol, antimullerian hormone, progesterone, inhibin B, activin

☑gametes

eggs or sperm

Endocrine disorders of the gonads affect the functioning of a number of other organs and organ systems besides the effects on the secondary sexual signal and reproductive function.

Hypogonadism can begin during fetal development, before puberty or during adulthood.

Signs and symptoms depend on when the condition develops.

Androgen deficiency during the second to third months of fetal development result in varying degrees of ambiguity of the genitalia and male pseudohermaphroditism.

☑ If the deficiency develops during the third trimester, defects in testicular descent leading to cryptorchidism as well as micropenis may occur.

☑ Prepubertal androgen deficiency leads too poor secondary sexual development and eunochoid skeletal proportions.

The penis fails to enlarge, the testes remain small, and the scrotum does not develop the marked rugea, charasteristic of puberty.

☑ If testosterone deficiency develops after puberty, the patinets complain of decreased libido, erectile dysfunction, and low energy.

Classified hypogonadism

- Primary hypogonadism (hypergonadotropic hypogonadism)
  - is typically caused by congenital differences affecting the gonads (e.g., Turner syndrome, Klinefelter syndrome) or acquired gonadal injury (e.g., irradiation, infection).
- Secondary/tertiery hypogonadism (hypogonadotropic hypogonadism)
  - is most often caused by pituitary or hypothalamic disorders (e.g, craniopharyngeoma, Kallmann syndrome).

- Following clinical evaluation, the diagnosis is confirmed with hormone tests, (LH, FSH, E2, T) and genetic testing may be considered.

The physiological function of the ovary

☑Hormone secretion

- sexual steroids-estrogens and progestins and androgenic hormones

☑Cytogenesis

- primordial follicles-primary, secondary and tertiary follicles

Estrogens (E2; estradiol; 17-beta (o)estradiol)

Estradiol is a steroid hormone made from cholesterol and is the strongest of the three naturally produced estrogens.

It is the main estrogen found in women and has many functions, although it mainly acts to mature and maintain the female reproductive system.

Roles

- Development of secondary sexuality
  - (breast formation, typical fat deposition, first menstruation)
- Mucosal proliferation
  - (normal menstrual cycle, sudden increase → LH peak, decrease → corpus luteum degeneration)
- They act on fertilization
- They prepare the breast for milk selection
- They affect the gonadotropic cells of the hypothalamus
- Lipoprotein metabolism, synthesis of plasma proteins, bone formation

Progesterone

Progesterone belongs to a group of steroid hormones called progestogens. It is mainly secreted by the corpus luteum in the ovary during the second half of the menstrual cycle. It plays important roles in the menstrual cycle and in maintaining the early stages of pregnancy.

Roles

- Secretory phase of the endometrium
  - (normal menstrual cycle)
- Maintenance of pregnancy-If the egg is fertilised
  - (preparation of the endometrium for the embryo)
  - progesterone stimulates the growth of blood vessels that supply the lining of the womb (endometrium) and stimulates glands in the endometrium to secrete nutrients that nourish the early embryo.
- Oviduct contraction
  - (transport to egg uterus)
- Increased viscosity of cervical mucus
  - (protective barrier)

- In the absence of corpus luteum hormone, it can occur only after the effect of estrogen
- Menarche averages 12.6 years
- On average 28 days, with follicle hormone dominant in the first half, corpus luteum hormone dominant in the second half

Estradiol levels vary throughout the monthly menstrual cycle, being highest at ovulation and lowest at menstruation.

Amenorrhea

- Amenorrhea (absence of menses) can be a transient, intermittent, or permanent condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus or vagina.
- It is often classified as either **primary** (absence of menarche by age 15 years or thereafter) or **secondary** (absence of menses for more than three months in girls or women who previously had regular menstrual cycles or six months in girls or women who had irregular menses

Prader-Willi-Labhardt syndrome (PWS) (can occur in both gender)

- Rare genetic, neurodevelopmental syndrome characterized by hypothalamic-pituitary dysfunction with severe hypotonia and feeding deficits during the neonatal period followed by an excessive weight gain period with hyperphagia with a risk of severe obesity during childhood and adulthood, learning difficulties
- 1:10 000-1:20 000 occurrence
- The syndrome is caused by absence of expression of the paternally active genes on the long arm of chromosome 15. The vast majority of cases occur sporadically.
- Clinical manifestation:
  - neonatal hypotonia
  - weak cry
  - genital hypoplasia, hypogonadism
  - behavioral issues are common problems
  - symptoms of hyperphagia with progressive development of obesity

Isolated gonadotropin-releasing hormone (GnRH) deficiency (idiopathic hypogonadotropic hypogonadism IHH)

- Isolated GnRH deficiency (also referred to as IHH) is a family of genetic disorders that are associated with defects in the production and/or action of hypothalamic peptide that controls human reproduction, GnRH.
- IHH can occur either with normal olfaction (normosmic IHH) or with anosmia. This latter clinical presentation of IHH with anosmia is referred to as Kallmann syndrome (KS)

Kallmann syndrome (KS)

- KS is a rare form of congenital isolated GnRH (gonadotropin-releasing hormone) deficiency characterized by low serum gonadotropin levels (LH and FSH) and by consequent sex steroids deficiency.
- It occurs as in 10 in 100000 boys and 2 in 100000 girls.
- The classic form is characterized by hypogonadotropic hypogonadism (lack of sexual maturity and absence of secondary sexual characteristics) with hyposmia or anosmia (decreased or absent smell) which is caused by failed migration of GnRH neurons from the olfactory placode into the brain (hypothalamus) during embryonic life.
- Mutations in more than 20 genes have been associated with KS. The first responsible gene found was *KAL1* that is associated with an X linked pattern of inheritance and its mutations occur especially in men with unilateral renal agenesis and mirror movements-bimanual synkinesis. *FGR1 (KAL2)* mutations are inherited as autosomal dominant traits and are associated with midline facial abnormalities cleft lip or palate, dental agenesis and short metacarpals or/and metatarsals.

Kallmann syndrome

- In women, secondary sexual characteristics are often completely absent, with little or no breast development or axillary hair.
- Men have little or no beard and body hair development, no increase in bulk of the muscles, and failure of the voice to deepen.
- In both sexes, some pubic hair can be present (adrenarche)
- Congenital abnormalities
  - Midline defects (ie, cleft lip/palate)
  - Anosmia/hyposmia
  - Unilateral renal agenesis
  - Uni- or bilateral cryptorchidism
  - Bimanual synkinesia (or mirror movements)
  - Syndactyly or other skeletal abnormalities
  - Hearing loss
  - Dental agenesis

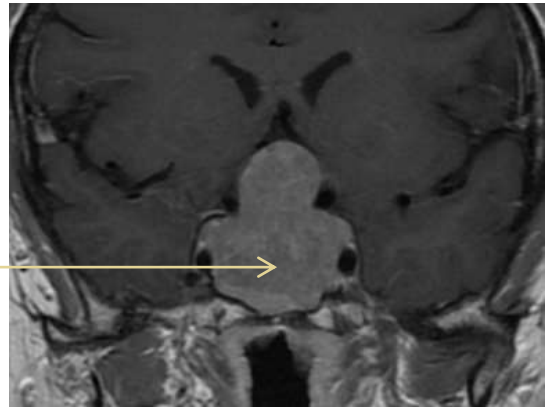
MANAGEMENT

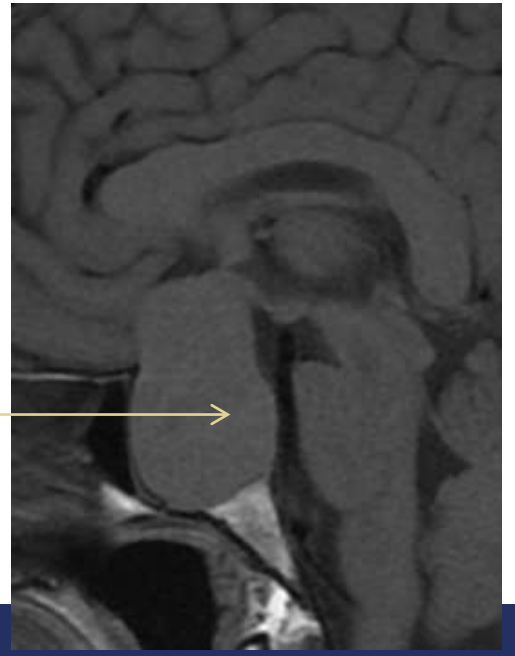
- The choice of therapy for IHH depends upon the patient's age and desire to achieve one or more of the following goals:

  - Induction of puberty and/or maintenance of sexual maturation
  - Induction or restoration of fertility
  - life-time sexual hormone replacement therapy is indicated for male patients, whereas in women it is proposed until the expected time of menopausa.

Hypogonadism resulting from pituitary gland

- Pituitary tumor and/or treatment
- Sheehan-syndrome
  (nowadays, it is rarer)
- injury (birth, traumatic brain injury)
- genetic reason (i.e mutation of the PROP gene)
- idiopathic
- Prolactinoma-hyperprolactinaemia (hypothyroidism)





Prolactinoma-hyperprolactinaemia

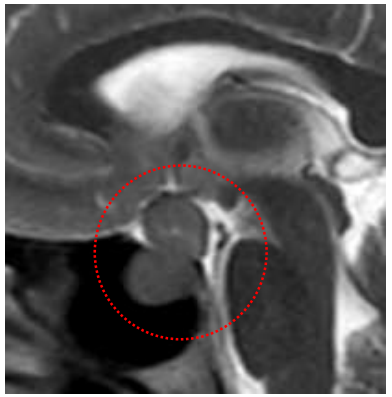
- galactrohhoea-amenorrhoea syndrome
- inhibition of LHRH secretion
- Causes
  - Pitutary tumor-prolactinoma
  - Primary hypothyreodism

    TSH↑ → PRL↑
  - Drug induced PRL↑

Treatment

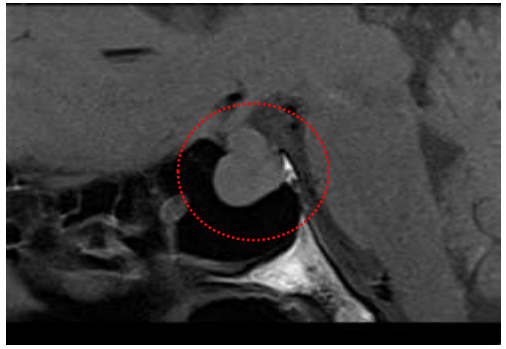
- Hypothyreodism- levothyroxin
- Hyperprolactinaemia, prolactinoma
  dopamin agonist

Regression of prolactinoma in a male by medication–dopamin agonist (bromocriptine)



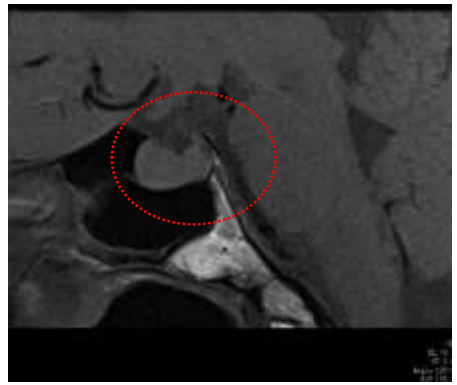
PROLACTINOMA INITIAL

PRL 395.20 ng/mL 1.20-10.70
Testosterone 1.95 ng/mL 2.80-8.00



IN 6 MONTHS

PRL: 54.60 ng/mL 1.20-10.70
Testosterone4.68 ng/mL 2.80-8.00



IN 12 MONTHS

PRL 34.93 ng/mL 1.20-10.70
Testosterone 6.09 ng/mL 2.80-8.00

Amenorrhea of ovarian origin/dysfunction

- Primary ovarian insufficiency (POI) is defined as the development of hypergonadotropic hypogonadism before the age of 40 years.
  - The presenting symptoms are similar to those of menopause
  - change in menstrual function (oligomenorrhea or amenorrhea),
  - elevated serum gonadotropins and low serum estradiol concentrations
  - estrogen deficiency symptoms such as hot flashes and vaginal dryness.
  - early diagnosis of POI is important for osteoporosis prevention
- Ovarialis dysgenesis-Turner-syndrome
- Polycystic ovarian syndrome (Stein-Leventhal syndrome)

Polycystic ovary syndrome
(Stein-Leventhal syndrome)

- **1935. Stein and Leventhal**
- The syndrome is heterogeneous clinically and biochemically
- manifest during adolescence, and is primarily characterized by ovulatory dysfunction and hyperandrogenism
- Increased risk for metabolic syndrome, type 2 diabetes mellitus, and possibly cardiovascular disease and endometrial carcinoma.
- a chief complaint of hirsutism, treatment-resistant acne, menstrual irregularity, acanthosis nigricans, and/or obesity.
- the most common cause of infertility in women

Diagnosis (PCOS)

- Symptoms
- Hormone levels
  - Androgens (testosterone), LH, FSH, (anti-müllerian hormone (AMH))
- transvaginal ultrasound

Rotterdam criteria (preferred) — Most expert groups use Rotterdam criteria to make the diagnosis of PCOS

Two out of three of the following criteria are required to make the diagnosis:

●Oligo- and/or anovulation

●Clinical and/or biochemical signs of hyperandrogenism

●Polycystic ovaries (by ultrasound)

PCOs treatment

Goals

- Amelioration of hyperandrogenic features (hirsutism, acne, scalp hair loss)
- Management of underlying metabolic abnormalities and reduction of risk factors for type 2 diabetes and cardiovascular disease
- Prevention of endometrial hyperplasia and carcinoma, which may occur as a result of chronic anovulation
- Contraception for those not pursuing pregnancy, as women with oligomenorrhea ovulate intermittently and unwanted pregnancy may occur
- Ovulation induction for those pursuing pregnancy

Treatment -Opportunities

- Lifestyle changes !!!!!!!!

  (diet, weight reduction

  if insulin resistance/type 2 diabetes: metformin)
- Oral contraceptives
- (antiandrogens)- spironolactone low dose
- Ovulation induction medications (clomiphen)
- Ovarian drilling
- In vitro fertilization

Tipical clinical features in TS

- Short stature 95-100%
- Growth failure 90-95%
- Increased upper-to-lower segment ratio >90%
- Defectiv dental development up to 75%
- Cubitus valgus 50%
- Kyphosis 50%
- Widely spaced niplles 70%
- Short neck 40%
- Genu valgum 35%
- Hight ached plate 35%
- Broad chest 30-35%
- Short metacrapals 35%
- Low posterior hairline 40%
- Webed neck 25%
- Infertility 95%
- Ovarian failure 90%
- Gonad dysgenesis 85-90%
- Cardiac malformation up to 50%
- Renal and renovascular malformations (horseshoe kidney) 20-30%
- Myopia, ptosis 10-50%
- Autoimmun thyreoditis 15-30%

Cardiovascular disease presents the most serious health problem for women with TS and substantially contributes to the increased mortality rates for affected individuals. The morbidity and mortality are due to increased risk for cardiovascular malformations, compounded by renal abnormalities and hypertension leading to increased risk for aortic dilatation and dissection.

Any malformation – Up to 50 percent
●Aortic valve abnormalities (primarily bicuspid aortic valve) – 15 to 30 %
●Elongated transverse aortic arch – 40 to 50 percent
●Other aortic arch abnormalities (primarily coarctation) – 7 to 18% ●Ventricular septal defects – 1 to 4 %
●Atrial septal defects – 1 to 2 %
●Systemic venous abnormalities (such as persistent left VCS) – 8 to 13 %
●Pulmonary venous abnormalities – 13 to 15 %
●Coronary artery abnormalities – Up to 2 %

TREATMENT IN TURNER SY

- Childhood: recombinant human growth hormone
- Adult:
  - hormone-replacement therapy (estradiol-progestin)
  - management of fertility

  (Spontaneous pregnancies are occasionally seen, and a number of women now undergo in vitro fertilization (IVF) with donor oocytes to try to conceive)
  - management of comorbidities
    - hypothyreodism, coeliac disease, CV

FEMALE HORMONE REPLACEMENT TREATMENT

- **Estrogen therapy** (if there is no uterus monotherapy)
- **Estrogen/progestin regimen** (intact uterus and require a progestin to prevent estrogen-induced endometrial hyperplasia and carcinoma)

  - Transdermal or vaginal delivery of estrogen are more physiologic approache (100 mcg daily or an estradiol vaginal ring 100 mcg)
  - oral estrogen (estradiol 0.5-2 mg daily)

  - micronized progesterone (MP) 200 mg per day for the first 12 days of the month or medroxyprogesterone acetate (MPA) (10 mg daily for 12 days per calendar month)
  - routine monitoring of serum estradiol levels not recommanded
  - Contraidication: endometrial cc, breast cc, liver damage.

Examination of male gonads

A Prader orchidometer for measuring testicular volume

- History
- Physical examination
- Semen analyses-WHO
  - After 5 days of carentia
  - Semen volume and pH
  - Microscopy for:
  - Sperm concentration, count, motility, and morphology
  - Debris and agglutination
  - Leukocyte count
  - Immature germ cells

Semen characteristic	Lower reference limit
Volume, mL	1.5
Sperm concentration, 10^6/mL	39
Total sperm number, 10^6	15
Total motility (PR + NP), %	40
Progressive motility (PR), %	32
Vitality (live spermatozoa), %	58
Sperm morphology (normal forms), %	4
pH	≥7.2
Seminal fructose, µmol/ejaculate	≥13

PR, progressive motility; NP, non-progressive motility.

Low circulating testosterone levels are associated with several detrimental health effects including **diminished libido, erectile dysfunction, loss of muscle and bone mass, increased visceral adiposity** (potentially yielding impaired glucose tolerance), melancholia (eventually culminating in depression) and **anemia**. Whether hypogonadism actually confers an enhanced risk for cardiovascular disease is still a matter of controversy.

Hypothalamic hypogonadism

- Kallman-syndrome
- Prader-Willi-syndrome
- Laurence-Moon-Biedl-syndrome
- Congenital (idiopatic) hypogonadotrop hypogonadism- IHH
  - 1:10 000, every 4-10 cases cryptorchism, sometimes micropenis, delayed puberty, small testis, eunuchoid body proportions, obesity, gynecomastia.
  - (LHRH treatment can induce puberty)

Pituitary causes (secundary) hypogonadism

- Idiopatic panhypopituitarism
- Pituitary tumor or/and treatment, Cushing sy. (cortisol excess-aromatase aktivity↑)
- Hyperprolactinaemia (inhibition of LHRH secretion)
- Pituitary gonadotrop secretion supression:
  - Congenital adrenal hyperplasia -CAH, estragen producing adrenal or Leydig cell-tumor, hCG-producing-testicular tumor, anabolic androgen exogen user, estrogen intake
- Selectiv FSH és LH deficiency
  - Mutaion of ß subunit gene

Treatment of hypogonadotrop hypogonadism

- Pituitary damage: androgen substitution and/or LH-FSH (childbearing potencial)

- LHRH deficiency: LH-RH (possibly clomiphen-citrat))
- HCG treatment (Leydig cell T producing)
- Hyperprolactinaemia: dopamin-agonist

Testicular (primary, hypergonadotrop) hypogonadism)

- Klinefelter syndrome is the most common cause of primary hypogonadism-gonadal dysgenesis
- The prevalence of Klinefelter syndrome is approximately 1 to 2.5 per 1000 boys and men (0.1 to 0.25 %).
- Only 25 to 50 % of patients with Klinefelter syndrome are diagnosed during their lifetimes
- 47,XXY, XXXY, XXXXY,XXYY
- The phenotype of Klinefelter is also affected by androgen responsiveness

Clinical features

- neonatal boy with micropenis, hypospadias, or cryptorchidism
- in teenage boys with delayed puberty
- men who present with small, testes and androgen deficiency or infertility
- gynecomastia, ED, osteporosis
- azoospermia
- very small, firm testes
- The most common morbidities
  - emphysema, COPD, T2DM, risk of breast cancer is up 50-fold higher, autoimmune diseases
- low serum total and free testosterone and high follicle-stimulating hormone (FSH)

Treatment-Care

- life-long testosteron replacement to prevent osteoporosis, obesity metabolic syndrome and diabetes is warranted
- KS patients might have reduced fertility. The advent of novel assisted reproductive techniques, such as the surgical extraction of sperm from testes (Testicular Extraction of Sperm (TESE) or microscopic TESE (microTESE) might help some KS patients to have children. This technique, however, must be done at such a young age as possible and the sperm should be cryopreserved
- due to numerous comorbidities, life-long care is needed.

XX testicular/ovotesticular disorder of sex development (DSD)

- rare
- XX testicular DSD is a term for conditions in which the gonads develop along the testicular rather than the ovarian pathway. The resulting gonad may be either a normal or a dysgenetic testis.
- gene exchange between the X and Y chromosomes (SRY). Regulatory gene suppressing the testicular gene of the X chromosome is transferred from Y to X
- Mutations in NR5A1
- Duplication of SOX9
- Inappropriate expression of SOX3

Testicular (primary/hypergonadotrop hypogonadism)

- Sertoli-cell only syndrome (Del Castillo-sy)
  - male azoospermia (1/10)
  - have microdeletions in the long arm of the Y chromosome
  - Testicular biopsies : germinal cell maturation arrest or Sertoli cell-only syndrome
  - FSH↑, LH, testosterone normal

Testicular (primary) hypergonadotrop hypogonadism

- Noonan-syndrome
  - Can occur in both gender
    - autosome dominant, cryptorchysm, testicular hypogonadism
    - like Turner sy stigmas (norenal disease and aortic stenosis)
    - Atrial septumdefect, valvular pulmonal stenosis
    - 46XY, 6-12 chromosome parcial deletion

Testicular (primary) hypergonadotrop hypogonadism

Myotonic dystrophy

- Myotonic dystrophy is an autosomal disorder with delayed onset (age 30 to 40 years) of impaired motor function
  - testicular hypogonadism, cataracts, premature frontal balding, mild mental retardation, and infertility

Kartagener-syndrome

- dynein defect -immobilized sperm
- situs inversus, bronchial disease

Testicular (primary) hypergonadotrop hypogonadism

- Acquired disorders of the testes
  - Radiation (> 2 Gy)
  - Environmental factors (lead, mercury, cadmium)
  - Pleasure drugs
  - Infection (viral orchitis, especially mumps)

Androgen insensitivity syndrome (AIS)

- In 1953 Morris wrote, the synonym: testicular feminisation
- Androgen receptor dysfunction
- disorder of sex development (DSD)
- due to mutations that cause impairment of androgen receptor (AR)
- Its phenotype is very different - it depends on residual androgen receptor activity
- inherited in an X-linked recessive fashion
- 46,XY individuals

Forms

- Complete androgen insensitivity syndrome (CAIS)
- Partial androgen insensitivity syndrome (PAIS)
- Mild androgen insensitivity syndrome (MAIS)

Testosterone treatment-
Which Form of Therapy?

- Oral administration of physiological testosterone has been proven unsuccessful due to extensive first pass metabolism through the liver despite having good gastrointestinal absorption

- Injection (Depo) (TE, TC, TU)
  - more comfortable
  - disadvantage-im injection
  - (SAE reactions of pulmonary oil microembolism and anaphylaxis)

- Transdermal form (gel)
  - the most physiological (diurnal rythm)
  - more consistent serum testosterone levels than other formulations
  - testosterone gel being transferred to females and children who come into contact with a patient's skin after use
  - for older patients (in this age group the risk of polycythemia is higher with injections than the risk with transdermal form gel)

Adverse effects of testosterone treatment

- Acne
- Oily skin
- Breast tenderness
- Decrease in HDL
- Injection pain/skin irritation
- Increase in , red blood cell, HTC
- Azoospermia
- Contraindication: prostate cancer, elevated liver function (3x) or liver neoplasm

Monitoring

- Testosteron levels (initially every 3 months then 6-12m)
  - For TU, levels should be measured prior to each subsequent injection
  - For gel- based on serum testosterone levels, the dose can be increased
- Hematocrit levels (6-12 months)
- Liver function (6-12 months)
- PSA (annually)
- Abdominal (liver) ultrasound (annually)

Thank you for the attention !

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