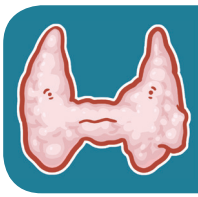

NOTES
GONADAL DYSFUNCTION

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Disturbance in gonadal development/function due to gonadal disorder/hypothalamic-gonadal axis dysfunction

CAUSES

- Impaired gonadal hormone production due to enzyme deficiency/receptor disturbance/exogenous hormone use
- Hypogonadotropic hypogonadism (AKA central/secondary hypogonadism)
  - Deficient gonadal hormone production due to decreased gonadotropin production
  - Gonadotropins, gonadal hormone levels low
- Hypergonadotropic hypogonadism (AKA peripheral/primary hypogonadism)
  - Deficient gonadal hormone production due to disease of gonads
  - Gonadotropin levels high, gondal hormone levels low

RISK FACTORS

- Genetic (autosomal dominant disease), history (gestational diabetes)
- Environment (e.g. obesity, lack of physical exercise, steroid use)

COMPLICATIONS

- Most commonly leads to infertility

SIGNS & SYMPTOMS

- Individuals who are biologically male
  - *Primary sex characteristic dysfunction:* small penis, testes; improper testicular descent; low sperm count
  - *Secondary sex characteristic dysfunction:* lack of facial, body hair; low muscle mass; failure of voice mutation
- Individuals who are biologically female
  - *Primary sex characteristic dysfunction:* amenorrhea (absence of menstruation), oligomenorrhea (irregular menstrual cycle)
  - *Secondary sex characteristic dysfunction:* lack of breast development, pubic hair

DIAGNOSIS

LAB RESULTS

- Blood tests
  - Gonadotropic, gonadal hormone levels

OTHER DIAGNOSTICS

- Tanner scale
  - Identify delayed development
  - Development of primary, secondary sex characteristics divided into five stages based on pubic hair, testicular volume, breast development

TREATMENT

OTHER INTERVENTIONS

- Hormone replacement therapy
- Infertility treatments

5-ALPHA-REDUCTASE DEFICIENCY

osms.it/5-alpha-reductase_deficiency

PATHOLOGY & CAUSES

- Autosomal recessive sex-limited genetic mutation in *SRD5A2* gene (encodes enzyme 5 alpha reductase)
- Defective/absent
- Affects only individuals who are biologically male
- Defective 5 alpha reductase → ↓ testosterone to dihydrotestosterone conversion → impaired secondary sexual characteristics development

COMPLICATIONS

- Infertility; inflammation, infection of gonads due to malformation

SIGNS & SYMPTOMS

Pre-puberty

- Male internal sex organs present, external genitalia with female appearance
  - Phallus doesn't fully elongate; resembles something between clitoris, penis
  - *Bifid scrotum:* scrotum remains split
  - *Hypospadias:* urethral opening remains on underside of penis
  - *Ambiguous genitalia:* external genitalia does not look clearly male/female

Puberty

- ↑ testosterone → despite no testosterone conversion, phallus, scrotum grow larger → male appearance, deepening of voice, muscle growth, development of facial, body hair

DIAGNOSIS

LAB RESULTS

- Genetic testing
  - Karyotyping to ensure individual genetically male; confirm enzyme deficiency
- Normal serum testosterone level, ↓ dihydrotestosterone levels, ↑ testosterone to dihydrotestosterone ratio

OTHER DIAGNOSTICS

- Suspected in newborns with ambiguous genitalia

TREATMENT

MEDICATIONS

- Hormone replacement therapy
  - Male/female sex hormones according to gender role adopted by individual

SURGERY

- Surgical procedures to help restore external genitalia to nonambiguous appearance

OTHER INTERVENTIONS

- Assisted reproduction techniques
  - Internal genitalia do not produce ova, may produce sperm

ANDROGEN INSENSITIVITY SYNDROME

osms.it/androgen-insensitivity

PATHOLOGY & CAUSES

- Genetic disorder of defective androgen receptor gene
- Person with XY genotype unresponsive to androgens
- Inherited in X-linked recessive pattern

TYPES

- Complete androgen insensitivity
  - Completely nonfunctional receptor; cells do not respond to androgens at all
- Partial androgen insensitivity
  - Some remaining function of androgen receptor; cells, tissues partially sensitive to androgens
- Mild androgen insensitivity
  - Masculinization of external genitalia

CAUSES

- Defect in androgen receptor on external genitalia, genital ducts, testes itself

COMPLICATIONS

- Infertility (most cases)
- Risk of testicular cancer due to cryptorchidism in complete androgen insensitivity

SIGNS & SYMPTOMS

Complete androgen insensitivity

- Cryptorchidism
  - Without effects of androgens, testes fail to descend into scrotum, remain in abdomen/pelvis
- Ineffective spermatogenesis
  - Epididymis, vas deferens, seminal vesicles do not develop normally
- Development of female secondary sex characteristics
  - Excess testosterone converted into estrogen → breast growth, widening of hips, female fat distribution
- Failed development of internal female organs
  - Testes still produce anti-Müllerian hormone → uterus, fallopian tubes do not develop, vagina ends in blind pouch → female appearance without menstrual cycles

Partial androgen insensitivity

- Appearance of external genitalia, secondary sex characteristics varies widely

Mild androgen insensitivity

- Masculinization of external genitalia, some female secondary sex characteristics

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Absence of uterus, ovaries; cryptorchidism

LAB RESULTS

- ↑ serum testosterone, dihydrotestosterone
- Genetic testing
  - Karyotype; visualize sex chromosomes, ensure individual genetically male

OTHER DIAGNOSTICS

- Diagnosed in infants with cryptorchidism
- Can remain undiagnosed until puberty

TREATMENT

MEDICATIONS

- Hormone replacement therapy
  - Male/female sex hormones according to gender role adopted by individual; testosterone/dihydrotestosterone if male, estrogen if female

SURGERY

- Surgical removal of testes (esp. in cryptorchidism) to reduce cancer risk
- External genitalia correction

DELAYED PUBERTY

osms.it/delayed-puberty

PATHOLOGY & CAUSES

- Onset of puberty after age 13 in individuals who are biologically female, after 14 in individuals who are biologically male

TYPES

Primary/hypergonadotropic hypogonadism

- Dysfunction of gonads due to unresponsiveness to luteinizing hormone (LH), follicle-stimulating hormone (FSH)/lack of testosterone/estrogen, progesterone production in gonads → no negative feedback on hypothalamus → overproduction of LH, FSH
- Causes of acquired
  - Radiation therapy, chemotherapy, trauma to gonads
- Causes of congenital
  - *Klinefelter syndrome:* two X chromosomes in individuals who are biologically male → small testes, sterility
  - *Turner syndrome:* X chromosome missing in individuals who are biologically female → dependence on hormonal treatment to develop secondary sex characteristics

Secondary/ hypogonadotropic hypogonadism

- Hypothalamus/pituitary gland dysfunction; inability to produce gonadotropin-releasing hormone (GnRH)/LH, FSH; suppression from other hormones (e.g. prolactin, thyroid hormone)
- Causes of acquired
  - Radiation therapy, chemotherapy, trauma to gonads, tumor of pituitary gland, hypothalamus
- Causes of congenital
  - Kallmann syndrome, panhypopituitarism
- General causes
  - Chronic illness (e.g. cystic fibrosis, celiac disease), excessive exercise, malnutrition/obesity, stress; affect hypothalamus, pituitary release of hormones

Constitutional delay

- Temporary delay in puberty; doesn't typically result in infertility
- Lack of GnRH, not pathologic → naturally slowed rate of maturation
- Onset of puberty occurs naturally, at later age; typically genetic component

COMPLICATIONS

- Permanent infertility if puberty never begins/fails to complete, sexual maturity never reached

SIGNS & SYMPTOMS

- Delayed primary, secondary sexual characteristics

DIAGNOSIS

LAB RESULTS

- Blood hormone levels
  - Indicate type of hypogonadism; ↓ testosterone, estrogen in low gonad activity; ↓ FSH, LH in suppressed pituitary activity

OTHER DIAGNOSTICS

- Medical history
  - Evaluate underlying medical conditions, family history for constitutional delay
- Tanner scale
  - Estimates puberty development

TREATMENT

MEDICATIONS

- Hormone replacement therapy

OTHER INTERVENTIONS

- Constitutional delay can resolve on own with natural onset of puberty
- Infertility treatments

KALLMANN SYNDROME

osms.it/kallmann-syndrome

PATHOLOGY & CAUSES

- Type of hypogonadotropic hypogonadism; delayed/absent puberty with impaired sense of smell (anosmia)
- Pituitary failure → ↓ sex hormones → hypogonadotropic hypogonadism → failure to start/complete puberty
- Defect in migration of neurons from olfactory placode
  - *Olfactory neurons:* hyposmia/anosmia (reduced sense of smell)
  - *GnRH neurons:* ↓ GnRH → ↓ LH, FSH

COMPLICATIONS

- Infertility, osteopenia, osteoporosis

SIGNS & SYMPTOMS

- Underdevelopment of primary, secondary sex characteristics; anosmia; long arms in proportion to body (eunuchoid body); osteoporosis; kidney agenesis
- Skeletal
  - Scoliosis, short middle finger, split hand/foot, teeth underdevelopment, cleft palate
- Neurological sensory, motor
  - Hearing impairment, colour blindness, dyskinesias, cerebral ataxia

DIAGNOSIS

LAB RESULTS

- Blood hormone levels
  - ↓ GnRH, LH, FSH, sex hormones
- Genetic tests
  - Gene mutation in *FGFR1*, *PROKR2*, *PROK2*, *CHD7*, *FGF8*; associated with Kallmann syndrome

OTHER DIAGNOSTICS

- Smell test, sperm count

TREATMENT

MEDICATIONS

- Hormone therapy
  - Stimulate puberty, development of secondary sex characteristics
- Calcium, vitamin D
  - Osteopenia

OTHER INTERVENTIONS

- Infertility treatments

POLYCYSTIC OVARY SYNDROME

osms.it/polycystic-ovary

PATHOLOGY & CAUSES

- Excessive androgen production by ovaries; primarily testosterone

CAUSES

Hyperinsulinemia

- Aids LH overproduction
- Theca cells in ovary express insulin receptors → excess insulin induces growth, division of theca cells → ↑ LH receptors → hypothalamus ↑ rate of GnRH pulses → ↑ LH secretion

Anterior pituitary produces excessive LH

- Theca cells produce excess amounts of androstenedione → converted into estrone by aromatase in adipose tissue → negative feedback signal → blocks anterior pituitary from releasing FSH, LH → no LH surge → no dominant follicle to break away from ovary → remains in ovary as cyst/ degenerates with other follicles → no ovulation

Excessive adipose tissue

- Aromatase in adipose tissue converts androgens to estrogens → ↑ androgens

RISK FACTORS

- *Genetic:* autosomal dominant disease
- Obesity, lack of physical exercise
- History of gestational diabetes

COMPLICATIONS

- Diabetes mellitus, hyperinsulinemia, infertility, increased risk of endometrial cancer

SIGNS & SYMPTOMS

- High levels of androstenedione → virilization
  - Excessive hair growth on chin, upper lip, chest, back (hirsutism)
  - Thinning of hair, from crown of head (male-pattern baldness)
  - Acne on face, chest, back
  - Lack of ovulation → oligomenorrhea, amenorrhea → infertility
- Insulin resistance
  - Overweight/obese; dark, velvety patches in creases of neck, groin, underarms (acanthosis nigricans)

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Follicles on one/both ovaries, appear like small cysts

LAB RESULTS

- Blood tests
  - ↑ LH to FSH ratio; ↑ androstenedione

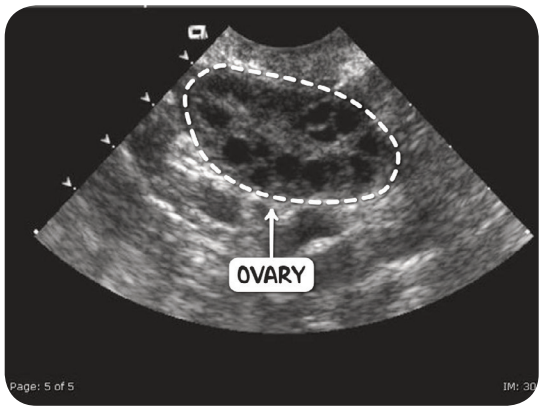

Figure 16.1 An abdominal ultrasound scan demonstrating a polycystic ovary. The cysts are are represented by the well circumscribed hypoechoic areas within the ovary.

OTHER DIAGNOSTICS

- Rotterdam criteria (2 of 3)
  - Lack of ovulation, excessive androgens, polycystic ovaries on ultrasound
- Oral glucose tolerance test (OGTT)
  - Establish insulin resistance

TREATMENT

MEDICATIONS

- Oral contraceptives
  - Regulate menstrual cycle
- Clomiphene citrate
  - Induce ovulation
- Metformin
  - Increase insulin sensitivity

SURGERY

- Ovarian drilling
  - Puncturing cystic ovary; induces ovulation; can damage ovary, doesn't resolve overall hormonal imbalance

OTHER INTERVENTIONS

- Incurable condition, treatment symptoms
- Weight loss, low glycemic index diet reduces insulin resistance, improves symptoms

PRECOCIOUS PUBERTY

osms.it/precocious-puberty

PATHOLOGY & CAUSES

- Onset of puberty at earlier age than average
  - ≤ eight in individuals who are biologically female, ≤ nine in individuals who are biologically male

TYPES

Central/gonadotropin-dependent precocious puberty

- Early maturation of hypothalamic-pituitary-gonadal axis → early release of LH, FSH → ↑ sex hormones
- Cause
  - *Dysfunctional hypothalamus/pituitary gland:* tumor releases GnRH/human chorionic gonadotropin (hCG); infection; cyst; radiation damage to brain → impairs negative feedback system in hypothalamic-pituitary-gonadal axis
  - *Idiopathic precocious puberty:* most common; normal variation; depends on weight, genetics

Peripheral/gonadotropin-independent precocious puberty

- Abnormal overproduction of sex hormones by testes/ovaries
- Cause
  - Ovarian/testicular cyst/tumor; genetic conditions (e.g. McCune–Albright syndrome); dysfunction of other glands (thyroid/adrenal gland); exogenous sex hormones from medications, creams

SIGNS & SYMPTOMS

- Child starts progressing through Tanner scale before 95% of other children at same age
- Early sexual maturation

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Structural abnormalities in brain

Ultrasound

- Screening of gonads

X-ray

- Estimates bone maturation

LAB RESULTS

- Gonadotropin hormone levels
  - Distinguish gonadotropin-dependent/independent causes

OTHER DIAGNOSTICS

- Physical exam
  - Assess growth compared to age; Tanner scale

TREATMENT

MEDICATION

- Hormone therapy
  - GnRH analogues → suppress hypothalamic-pituitary-gonadal axis hormones, bind to GnRH receptor on pituitary gland → decrease release of LH, FSH → slow puberty

SURGERY

- Surgical removal of tumor/cyst from ovaries/testicles

PREMATURE OVARIAN FAILURE

osms.it/premature-ovarian-failure

PATHOLOGY & CAUSES

- AKA primary ovarian insufficiency
- Loss of function of ovaries before age 40; not caused by menopause
- Follicles stop responding to pituitary LH, FSH → disrupted ovulation → ↓ estrogen, progesterone, androstenedione → amenorrhea, hypogonadotropism, hypoestrogenism
- Around half of biologically-female individuals maintain some intermittent ovarian function
- Usually no clear cause; associated with
  - *Acquired:* chemotherapy, radiotherapy, autoimmune destruction
  - *Genetic:* Turner syndrome, fragile X syndrome, *BRCA1* mutations → gonadal dysgenesis
- Two mechanisms
  - *No remaining follicles:* ovary started off with few/rapid degeneration
  - *Follicles dysfunctional:* hypergonadotropic hypogonadism; estrogen-low pituitary increases LH, FSH production

COMPLICATIONS

- Infertility, cardiovascular disease, osteoporosis, hypothyroidism, Addison's disease

SIGNS & SYMPTOMS

- Absence of ovulation; low levels of estrogen, progesterone
- Normal puberty with regular periods before disorder develops
- Infrequent menstrual periods → difficulty conceiving/infertility
- *Lack of hormones:* hot flashes, night sweats, vaginal dryness → dyspareunia (pain during sex)
- ↓ *estrogen:* cardiovascular disease, osteoporosis, decreased bone density
- Symptoms mimic natural menopause; some biologically-female individuals still able to get pregnant due to intermittent ovarian function

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Shrunken ovaries

LAB RESULTS

- ↓ ovarian hormones (estrogen), ↑ LH, FSH
- If autoimmune cause suspected
  - Test for steroid cell antibodies/ sulfoxythiocarbamate alkynes (STCAs)
- Genetic testing
  - Karyotype, chromosomal abnormalities; evaluate for genetic disease

TREATMENT

MEDICATIONS

- Hormone replacement therapy
  - Estrogen, progesterone

OTHER INTERVENTIONS

- In-vitro fertilization
  - Treat infertility