GONADAL DYSGENESIS
Dysgenetic Gonads, Ovarian Dysgenesis, Streak Gonads

Any congenital developmental disorder of the reproductive system characterized by a progressive loss of germ cells on the developing gonads.

Related Diagnoses:
- Undescended testes
- Turner syndrome
- XX male syndrome
- Premature ovarian failure
- Testicular failure
- Y-chromosome deletions
- Swyer syndrome

About Gonadal dysgenesis

Gonadal dysgenesis is a term used for a unique subset of disorders of sexual development characterized by incomplete or defective formation of the gonads (ovary or testis) due to either structural or numerical anomalies of the sex chromosomes or mutations in the genes involved in the development of the gonad.

Gonadal dysgenesis can be classified depending on the gonadal morphology as:

- **Complete gonadal dysgenesis (CGD)** - no gonadal development occurs, and, as a consequence, patients have a completely female phenotype due to the lack of any gonadal steroid production.
- **Partial gonadal dysgenesis (PGD)** - Y chromosome is present, there is incomplete testis determination and the external observable characteristics or traits (phenotype) depend on the degree of testicular function.

The gonadal dysgenesis will occur if there is an absence of both antimüllerian hormone (AMH) and testosterone. The absence of testosterone will result in regression of the Wolffian ducts; normal male internal reproductive tracts will not develop. The absence of AMH will allow the Müllerian ducts to differentiate into the oviducts and uterus. In sum, this individual will possess female-like internal and external reproductive characteristics, lacking secondary sex characteristics, i.e. underdeveloped sex organs and ambiguous genitalia (sexual organs that aren’t well formed or aren’t clearly male or female).

In a normal situation, all the cells in an individual will have 46 chromosomes with one being an X and one a Y (Pic. 1) or with two X chromosomes. However, sometimes during this complicated early copying process (DNA replication and cell division), one chromosome can be lost.

Depending on the number and appearance of chromosomes (karyotype), gonadal dysgenesis is classified into:

- **XO gonadal dysgenesis (45,XO)** – Turner syndrome
- **XX gonadal dysgenesis (46,XX)**
- **XY gonadal dysgenesis (46,XY)** – Swyer syndrome
- **XO/XY mosaicism (45,X/46,XY)** – mixed gonadal dysgenesis

**XO gonadal dysgenesis (Turner syndrome)**

XO (45,X) gonadal dysgenesis, also called Turner syndrome (Pic. 2), may be defined as the combination of phenotypic features and complete or partial absence of one of the X chromosomes (monosomy) that is the cause of the development of gonadal dysgenesis.

In most cases, Turner syndrome is a sporadic event, and for the parents of an individual with Turner syndrome the risk of recurrence is not increased for subsequent pregnancies. Rare exceptions may include the presence of
a balanced translocation of the X chromosome in a parent, or where the mother has 45,X mosaicism restricted to her germ cells.

Turner syndrome can be diagnosed postnatally at any age. Often, it is diagnosed at birth due to heart problems, an unusually wide neck or swelling of the hands and feet. However, it is also common for it to go undiagnosed for several years, typically until the girl reaches the age of puberty/adolescence and she fails to develop properly (the changes associated with puberty do not occur). In childhood, a short stature can be indicative of Turner syndrome.

A test, called a karyotype or a chromosome analysis, analyzes the chromosomal composition of the individual. This is the test of choice to diagnose Turner syndrome. Rare exceptions may include the presence of a balanced translocation of the X chromosome in a parent, or where the mother has 45,X mosaicism restricted to her germ cells.

**XX gonadal dysgenesis**

In XX gonadal dysgenesis, no functional ovaries are present to induce puberty in an otherwise normal girl whose karyotype is found to be 46,XX. With nonfunctional streak ovaries she is low in estrogen levels (hypoestrogenic) and has high levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Because of the inability of the streak gonads to produce sex hormones (both estrogens and androgens), most of the secondary sex characteristics do not develop.

The cause of the condition is often unclear. There are cases where abnormalities in the FSH-receptor have been reported. Apparently either the germ cells do not form or interact with the gonadal ridge (precursor to the gonads) or undergo accelerated atresia (absence or closure of a natural passage of the body) so that at the end of childhood only a streak gonad is present, unable to induce pubertal changes. As girls' ovaries produce no important body changes before puberty, there is usually no suspicion of a defect of the reproductive system until puberty fails to occur. Familial cases of XX gonadal dysgenesis are on record.

**XY gonadal dysgenesis (Swyer syndrome)**

XY gonadal dysgenesis, or Swyer syndrome, is a type of hypogonadism (testes or the female ovaries produce little or no sex hormones) where a person is externally female (although have XY chromosomes instead of XX; Pic. 3) with streak gonads, and if left untreated, will not experience puberty.

The first known step of sexual differentiation of a normal XY fetus is the development of testes. The early stages of testicular formation in the second month of gestation requires the action of several genes, of which one of the earliest and most important is SRY, the sex-determining region of the Y chromosome. Mutations of SRY account for many cases of Swyer syndrome.

When such a gene is defective, the indifferent gonads fail to differentiate into testes in an XY (genetically male) fetus. Without testes, no testosterone or antimüllerian hormone (AMH) is produced. Without testosterone, the Wolffian ducts (paired ducts in the embryo) fail to develop, so no internal male organs are formed. Also, the lack of testosterone means that no dihydrotestosterone is formed and consequently the external genitalia fail to virilize, resulting in normal female genitalia. Without AMH, the Müllerian ducts develop into normal internal female organs (uterus, fallopian tubes, cervix, vagina).

A baby who is externally a girl is born and is normal in all anatomic respects except that the child has nonfunctional streak gonads instead of ovaries or testes. As girls' ovaries normally produce no important body changes before puberty, a defect of the reproductive system typically remains unsuspected until puberty fails to occur in people with Swyer syndrome. They appear to be normal girls and are generally considered so.

Evaluation of delayed puberty usually reveals elevation of gonadotropins, indicating that the pituitary is providing the signal for puberty but the gonads are failing to respond. The next steps of the evaluation usually include checking a karyotype and imaging of the pelvis. The karyotype reveals XY chromosomes and the imaging demonstrates the presence of a uterus but no ovaries (the streak gonads are not usually seen by most imaging). Although an XY karyotype can also indicate a person with complete androgen insensitivity syndrome, the absence of breasts, and the presence of a uterus and pubic hair exclude the possibility.

**X0/XY mosaicism (mixed gonadal dysgenesis)**

In 45,X/46,XY, most or all of the Y chromosome is lost in one of the newly-created cells. All the cells then made
There are many chromosomal variations that cause the 45,X/46,XY karyotype, including malformation (isodentricism) of the Y chromosomes, deletions of Y chromosome or translocations of Y chromosome segments. These rearrangements of the Y chromosome can lead to partial manifestation of a gene (expression) of the SRY gene which may lead to abnormal genitals and testosterone levels.

**Associated diseases**

- complete androgen insensitivity syndrome
- partial X chromosome deletions
- lipoïd congenital adrenal hyperplasia - disease that results from defects in steps of the synthesis of steroid hormones from cholesterol
- cardiorenal syndrome - disorders of the heart and kidneys
- Denys-Drash syndrome – kidney disease
- Wilm's tumors – kidney cancer
- osteoporosis – decreased bone strength associated with Turner syndrome
- Perrault syndrome - XX gonadal dysgenesis + sensorineural hearing loss

**Complications**

Gonadal dysgenesis is associated with the development of gonadoblastoma, a tumor containing nests of germ cells and cells resembling Sertoli or granulosa cells. The risk has been previously estimated to be up to 30%. The pathogenesis of gonadoblastomas and their malignant potential are still rather obscure, but the tumor is frequently associated with other malignant forms such as dysgerminomas (type of germ cell tumor).

**Other common complications include:**

- impaired fertility or infertility
- ambiguous genitalia
- primary amenorrhea (absence of menstrual cycle) in Swyer syndrome
- ovarian failure
- miscarriages
- stillbirths
- malformed babies
- delayed puberty
- webbed neck
- narrow aorta
- streak gonads

**Risk factors**

- high level of LH
- low level of FSH
- environmental endocrine disruptors - chemicals that can interfere with endocrine (or hormone) systems

**Impact on fertility**

Gonadal dysgenesis is characterized by incomplete or defective formation of the gonads (ovary or testis) where there are always no or lack ovaries, small uterus and undescended testes in males in some forms. As a result, infertility is often seen. Women don’t produce any own eggs (no ovaries), but have uterus and it is possible to give birth after assisted reproductive technology (ART) treatment for those patients. Additionally, only 2% of Turner syndrome patients have natural pregnancies, with high rates of miscarriages, stillbirths and malformed babies.

Men have immaturesd seminiferous tubules where spermatozoa are created. Thus, men with gonadal dysgenesis have limited count of undifferentiated male germ cell (spermatogonia), if they have any, that may be used in ART treatment of infertility.

**Prevention**
There is no primary prevention to prevent gonadal dysgenesis. The disorders occur randomly and are not inherited. They may be prenatally diagnosed by amniocentesis or chorionic villus sampling except mixed gonadal dysgenesis that is very difficult to diagnose prenatally. Although the recurrence risk is not increased, genetic counseling is often recommended for families who have had a pregnancy or child with gonadal dysgenesis. Usually, fetuses with Turner syndrome can be identified by abnormal ultrasound findings (i.e., heart defect, kidney abnormality, cystic hygroma, ascites).

**Symptoms**

The loss of germ cells on the developing gonads of an embryo leads to extremely hypoplastic (underdeveloped) and dysfunctioning gonads mainly composed of fibrous tissue, hence the name streak gonads - i.e., a form of aplasia in which the ovary is replaced by functionless tissue. The accompanying hormonal failure also prevents the development of secondary sex characteristics in either sex, resulting in a sexually infantile female appearance and infertility.

**Secondary sex characteristics that are affected in gonadal dysgenesis patients include:**

**In females:**

- enlargement of breasts and erection of nipples
- growth of body hair, most prominently underarm and pubic hair
- greater development of thigh muscles behind the femur, rather than in front of it
- widening of hips; lower waist to hip ratio than adult males
- smaller hands and feet than male adults
- elbows that hyperextend 5-8° more than male adults
- rounder face
- smaller waist than male adults
- upper arms approximately 2 cm longer, on average, for a given height
- changed distribution in weight and fat; more subcutaneous fat and fat deposits, mainly around the buttocks, thighs, and hips
- labia minora (the inner lips of the vulva) may grow more prominent and undergo changes in color

**In males:**

- growth of body (underarm, abdominal, chest hair and pubic) and facial hair
- larger stature
- enlargement of larynx (Adam's apple) and deepening of voice
- heavier skull and bone structure
- increased muscle mass and strength
- larger hands, feet and nose than females and prepubescent males
- square face
- small waist, but wider than females
- broadening of shoulders and chest; shoulders wider than hips
- increased secretions of oil and sweat glands, often causing acne and body odor
- coarsening or rigidity of skin texture due to less subcutaneous fat
- enlargement (growth) of the penis

**Therapies**

**Self therapy**

Psychological support

Psychological support should be helpful to patients and their families for better coping with the disease.
Conventional medicine

Pharmacotherapy

Hormone replacement therapy (HRT)

Upon diagnosis of gonadal dysgenesis, estrogen and progesterone therapy is typically commenced, promoting the development of normal female sexual characteristics and to prevent cardiovascular complications and osteoporosis. Human growth hormone injections during childhood may increase adult height. Estrogen replacement therapy can promote development of the breasts and hips. Estrogen therapy does not make a woman with nonfunctional ovaries fertile, but it plays an important role in assisted reproduction; the health of the uterus must be maintained with estrogen if an eligible woman with Turner Syndrome wishes to use IVF (using donated eggs).

Patients with mixed gonadal dysgenesis receive hormone replacement therapy depending on their gender. Males need treatment depending on level of testicular insufficiency.

Surgical therapy

Gonadectomy

To prevent the development of malignancy in patients with XY gonadal dysgenesis, gonadectomy typically is recommended. In mixed gonadal dysgenesis, deciding on a sex assignment depends on the anatomic findings, so it will vary from child to child. Corrective surgery is needed most cases because the two gonads do not match up. If you raise the child a male, the female ductal structures on the opposite side would need to be removed. If you raise the child as a female, because the phallus is small and the likelihood is that she would function better as a female, then the testis would need to be removed.

Assisted reproduction

Assisted reproductive technology (ART) is the technology used to achieve pregnancy in procedures such as fertility medication, artificial insemination, in vitro fertilization and surrogacy.

Gonadal dysfunction among women with gonadal dysgenesis has been regarded as a major indication for egg donation due to lack of own ovaries. Other option for those women that cannot produce own eggs is surrogacy via a gestational carrier.

The preimplantation genetic screening/preimplantation genetic diagnosis (PGS/PGD) allows studying the DNA of eggs or embryos to select those that carry certain damaging characteristics. It is useful when there are previous chromosomal or genetic disorders in the family, within the context of in vitro fertilization programs.

Rapidly evolving genomic technology is used to screen 1st trimester pregnancies for sex chromosomal anomalies. The preimplantation genetic screening/preimplantation genetic diagnosis (PGS/PGD) allows studying the DNA of eggs or embryos to select those that carry certain damaging characteristics. It is useful when there are previous chromosomal or genetic disorders in the family, within the context of in vitro fertilization programs.
Undescended testes
In the case of cryptorchidism one or both testes are absent from the scrotum. It is is the most common etiologic factor of azoospermy in the adult.
Learn more at: www.fertilitypedia.org/therapy/diag/undescended-testes

Turner syndrome
Turner syndrome is a genetic disorder in which a female is partly or completely missing one X chromosome that results in ovarian dysgenesis.
Learn more at: www.fertilitypedia.org/therapy/diag/turner-syndrome

XX male syndrome
The male sex chromosomal disorder characterized by a spectrum of clinical presentations, ranging from ambiguous to normal male genitalia.
Learn more at: www.fertilitypedia.org/therapy/diag/xx-male-syndrome

Premature ovarian failure
The loss of function of the ovaries before age 40.
Learn more at: www.fertilitypedia.org/therapy/diag/premature-ovarian-failure

Testicular failure
The inability of the testicles to produce sperm or testosterone.
Learn more at: www.fertilitypedia.org/therapy/diag/testicular-failure

Y-chromosome deletions
A family of genetic disorders caused by missing gene(s) in the Y chromosome.
Learn more at: www.fertilitypedia.org/therapy/diag/y-chromosome-deletions

Swyer syndrome
A rare disorder characterized by a phenotypic female with an XY karyotype.
Learn more at: www.fertilitypedia.org/therapy/diag/swyer-syndrome

⚠️ Risk factors

High level of LH
A condition with high blood luteinizing hormone (LH) leading to irregular periods and reduced fertility in both females and males.
Learn more at: www.fertilitypedia.org/therapy/ri/high-level-of-lh

Low level of FSH
A condition with low serum follicle-stimulating hormone (FSH) concentration.
Learn more at: www.fertilitypedia.org/therapy/ri/low-level-of-fsh

🔍 Symptoms

Increased level of FSH
A condition with high serum follicle-stimulating hormone (FSH) concentration.
Learn more at: www.fertilitypedia.org/edu/symptoms/increased-level-of-fsh

💡 Therapies

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation
ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: [www.fertilitypedia.org/edu/therapies/icsi](http://www.fertilitypedia.org/edu/therapies/icsi)

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: [www.fertilitypedia.org/edu/therapies/sperm-donation](http://www.fertilitypedia.org/edu/therapies/sperm-donation)

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: [www.fertilitypedia.org/edu/therapies/standard-ivf](http://www.fertilitypedia.org/edu/therapies/standard-ivf)

Gallery

| Pic | Pic. 2: Karyotype in Turner syndrome
45,X karyotype, showing an unpaired X at the lower right. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Sources


"Screening of Y chromosome microdeletions in 46,XY partial gonadal dysgenesis and in patients with a 45,X/46,XY karyotype or its variants" ([http://bmcmedgenet.biomedcentral.com/articles/10.1186/1471-2350-14-115](http://bmcmedgenet.biomedcentral.com/articles/10.1186/1471-2350-14-115)) —by Santos et al. licensed under [CC BY 2.0](http://creativecommons.org/licenses/by/2.0/)

"Gonadal dysgenesis" ([https://en.wikipedia.org/wiki/Gonadal_dysgenesis](https://en.wikipedia.org/wiki/Gonadal_dysgenesis)) —sourced from Wikipedia licensed under [CC BY-SA 3.0](http://creativecommons.org/licenses/by-sa/3.0/)

"Assisted reproductive technology" ([https://fertilitypedia.org/edu/therapies/assisted-reproductive-technology](https://fertilitypedia.org/edu/therapies/assisted-reproductive-technology)) —sourced from Fertilitypedia licensed under [CC BY-SA 4.0](http://creativecommons.org/licenses/by-sa/4.0/)


"45,X/46,XY mosaicism" ([https://en.wikipedia.org/wiki/45,X/46,XY_mosaicism](https://en.wikipedia.org/wiki/45,X/46,XY_mosaicism)) —sourced from Wikipedia licensed under [CC BY-SA 3.0](http://creativecommons.org/licenses/by-sa/3.0/)
“Turner syndrome: counseling prior to oocyte donation” — by Ramos licensed under CC BY-NC 4.0

“XX gonadal dysgenesis” —sourced from Wikipedia licensed under CC BY-SA 3.0

“Long-Term Follow-Up of Patients with 46,XY Partial Gonadal Dysgenesis Reared as Males” — by de Andrade et al. licensed under CC BY 3.0

“Recent Developments in Diagnosis and Care for Girls in Turner Syndrome” — by Bondy licensed under CC BY 3.0

“Secondary sex characteristic” —sourced from Wikipedia licensed under CC BY-SA 3.0

“45,X” —sourced from Wikipedia licensed under CC BY 2.0

“Mixed Germ Cell Tumour in a Case of Pure Gonadal Dysgenesis (Swyer Syndrome) - A Case Report” — by Kumar et al. licensed under CC BY 3.0

“Human male karyotype high resolution - Y chromosome” —by National Human Genome Research Institute licensed under CC0 1.0