HYPOPITUITARISM

Partial or complete loss of production of one or more of the pituitary gland hormones.

About Hypopituitarism

Hypopituitarism refers to decreased secretion of pituitary hormones as a result of abnormalities in the pituitary itself or the hypothalamus. If there is decreased secretion of most pituitary hormones, the term panhypopituitarism is used.

The pituitary gland hormones are:

**anterior**
- adrenocorticotropic hormone (ACTH) - acts on adrenal glands to secrete steroid hormones such as cortisol
- growth hormone (GH) - increases growth and metabolism
- luteinizing hormone (LH) and follicle stimulating hormone (FSH) - act on the ovaries or testes to produce the relevant sex hormone as well as egg or sperm maturity
- prolactin (PRL) - acts on breasts to produce milk
- thyroid stimulating hormone (TSH) - acts on the thyroid gland to produce thyroid hormones

**posterior (produced in hypothalamus)**
- anti-diuretic hormone (ADH) - Acts on collecting ducts of the kidneys to increase water reabsorption for regulating of water balance and blood pressure
- oxytocin - acts on the uterus to cause contractions during labour and on breast ducts to cause lactation that also increases bonding between individuals
The pathophysiology of hypopituitarism is varied because of its multiple causes and presentations due to different hormones being affected. In most of the cases, three or more hormones are deficient. Generally, the finding of a combination of a low pituitary hormone together with a low hormone from the effector gland (responds to a hormonal stimulus) is indicative of hypopituitarism. Occasionally, the pituitary hormone may be normal but the effector gland hormone decreased; in this case, the pituitary is not responding appropriately to effector hormone changes, and the combination of findings is still suggestive of hypopituitarism.

It usually occurs due to a pituitary tumor or as a consequence of its treatment, and symptoms vary depending on which hormone is deficient. It is, however, important to remember that pituitary tumors can cause hypopituitarism due to structure compression. The most common problem is insufficiency of follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH) leading to sex hormone abnormalities. Growth hormone deficiency is more common in people with an underlying tumor than those with other causes.

Diagnosis is made based on blood biochemical tests showing hormonal deficits. Two types of blood tests are used to confirm the presence of a hormone deficiency:

- basal levels - blood samples are taken (usually in the morning) without any form of stimulation
- dynamic tests - blood tests are taken after the injection of a stimulating substance

Measurement of ACTH and growth hormone usually requires dynamic testing, whereas the other hormones (LH/FSH, prolactin, TSH) can typically be tested with basal levels. There is no adequate direct test for ADH levels, but ADH deficiency can be confirmed indirectly; oxytocin levels are not routinely measured.

If one of these tests shows a deficiency of hormones produced by the pituitary, magnetic resonance imaging (MRI) scan of the pituitary is the first step in identifying an underlying cause. MRI may show various tumors and may assist in delineating other causes.

Other tests that may assist in the diagnosis of hypopituitarism, especially if no tumor is found on the MRI scan, are ferritin (elevated in hemochromatosis), angiotensin converting enzyme (ACE) levels (often elevated in sarcoidosis), and human chorionic gonadotropin (often elevated in tumor of germ cell origin). If a genetic cause is suspected, genetic testing may be performed, but these causes are very rare. Inheritance patterns may be autosomal recessive (both parents carry and pass on a defective gene to their child), autosomal dominant (normal gene from one parent and a defective gene from the other
parent), or X-linked recessive (gene that causes the trait or the disorder is located on the X chromosome), but most of the mutation cases are de novo (not inherited).

**Mutation in those genes causes hypopituitarism:**

- HESX1 – associated with septo-optic aplasia (SOD), combined pituitary hormone deficiency (CPHD) and isolated growth hormone deficiency (IGHD)
- transcription factor SOX3 (SRY-related HMG-box)
- LHX3 (LHX3 LIM homeobox 3) – recessive phenotype characterized by GH, TSH, LH and FSH deficiency, short stiff neck with limited rotation
- LHX4 (LHX4 LIM homeobox 4) - dominantly inherited and associated with GH, TSH and ACTH deficiency
- PROP1 (pituitary-specific transcription factor) - recessive mutations associated with GH, PRL and TSH deficiency with additional LH and FSH deficiency
- POU1F1 (POU Class 1 homeobox 1) - GH, TSH and prolactin deficiency, the TSH deficiency being highly variable

Treatment of hypopituitarism is threefold: removing the underlying cause, treating the hormone deficiencies, and addressing any other repercussions that arise from the hormone deficiencies.

**Associated diseases**

- hypogonadism - diminished functional activity of the gonads
- syphilis
- cardiovascular disease
- lung diseases
- atherosclerosis - artery-wall thickens
- osteoporosis – bone fragility
- hypothyroidism – deficiency of thyroid hormone
- Addison’s disease - cortisol deficiency as the result of direct damage to the adrenal glands
- dyslipidemia - abnormal amount of lipids in the blood
- diabetes mellitus
- arthrogryposis, distal, with hypopituitarism, mental retardation, and facial anomalies
- autoimmune hypophysitis - inflammation of the pituitary gland due to autoimmunity
- Froelich’s syndrome – condition associated with low levels of GnRH
gigantism
- granulomatous hypophysitis - chronic inflammatory of the enlarged pituitary gland
- hypothalamic hamartomas - tumor-like malformations that occur during fetal development
- RHYNS syndrome - eye, kidney and skeletal abnormalities
Complications

- poor pregnancy rate
- high miscarriage rate
- abortion
- anemia
- pregnancy-induced hypertension – high blood pressure during pregnancy
- placental abruption
- premature birth
- postpartum uterine inertia leading to postpartum bleeding (hemorrhage)
- insufficient milk production
- infertility (hypogonadism)
- anovulation – ovaries don’t release the egg

growth hormone deficiency:

- obesity
- raised cholesterol
- metabolic syndrome

estradiol deficiency:

- osteoporosis - decreased bone strength
- thyroid hormone deficiency:
  - failure in fetal brain development

Risk factors

- head or brain injury
- brain tumor
- brain infections
- radiotherapy
- stroke
- tuberculosis
- uncommon diseases, such as sarcoidosis and histiocytosis X
- type 1 diabetes

Impact on fertility

Infertility in hypopituitarism patients is caused by LH and FSH deficiency leading to sex hormone abnormalities and insufficient egg and sperm maturation. In men, a hormone replacement treatment for one year or more is needed to achieve a sperm count adequate to father a baby.

Unexplained infertility may be a result of growth hormone deficiency due its
role in reproductive system. In men, it controls male sexual maturation and adult reproductive function. It affects gonadal differentiation, steroidogenesis (steroid hormones production by ovaries, testes and brain), gametogenesis (gamete formation), and gonadotropin secretion and responsiveness. In women, it acts as a modulator on gonadotropins and follicular maturation. So, growth hormone deficiency may be tested as a possible cause of unexplained infertility.

Before pregnancy, the hormone levels should be restored to normal level. Pregnancies resulting from fertility treatment of hypopituitarism are associated with an increased risk of pregnancy complications such as abortion, anemia, pregnancy-induced hypertension, placental abruption, premature birth, and postpartum hemorrhage. In those patients, close monitoring is necessary as changes may need to be made to their medications. Ultrasounds measurement is also needed for fetal growth assessment.

**Prevention**

In most cases, the disorder is not preventable because most of the cases are after delivery. Hypopituitarism requires lifelong treatment with one or more medicines. For patients, regular follow-up is essential to prevent adverse outcomes in emergency situations. Wearing a medical alert bracelet or carrying an identify card with details of disorder and medicines.

Risk of hypopituitarism occurring after delivery can be minimized by taking proper obstetric care.

**Symptoms**

*Depends on hormone which is deficient:*

- growth hormone - central obesity, muscle weakness, impaired attention and memory, growth retardation, short stature and more
- gonadotropins (FSH and LH) - amenorrhea (absence of a menstrual period), erectile dysfunction, infertility, failure to have puberty, decreased libido and other symptoms and more
- thyroid stimulating hormone (hypothyroidism) - weakness, fatigue, insensitivity to cold, weight gain, abnormal menstruation and other symptoms and more
- adrenocorticotrophin - no skin pigmentation unlike primary adrenal insufficiency (skin pigmentation is due to high ACTH), delayed puberty,
Fatigue, anorexia, weight loss and other symptoms and more
- Prolactin - inability to breastfeed
- Anti-diuretic hormone - diabetes insipidus (inability to concentrate the urine), polyuria (production of large amounts of clear urine), hypernatremia (high sodium levels in the blood)
- Oxytocin - few symptoms, as it is only required at the time of childbirth and breastfeeding

Therapies

Self therapy

There is no self or alternative therapy for hypopituitarism treatment.

Conventional medicine

Pharmacotherapy

Hormone replacement therapy (HRT)

Most pituitary hormones can be replaced indirectly by administering the products of the effector glands that response to stimulus of hormone deficiency: hydrocortisone (cortisol) for adrenal insufficiency, levothyroxine for hypothyroidism, testosterone for male hypogonadism, and estradiol for female hypogonadism (usually with a progestogen to inhibit unwanted effects on the uterus).

Growth hormone is available in synthetic form, but needs to be administered parenterally (by injection). Antidiuretic hormone can be replaced by desmopressin (DDAVP) tablets or nose spray. Generally, the lowest dose of the replacement medication is used to restore wellbeing and correct the deranged results, as excessive doses would cause side-effects or complications. Those requiring hydrocortisone are usually instructed to increase their dose in physically stressful events such as injury, hospitalization and dental work as these are times when the normal supplementary dose may be inadequate, putting the patient at risk of adrenal crisis.

Difficult situations arise in deficiencies of the hypothalamus-pituitary-
gonadal axis in people (both men and women) who experience infertility; infertility in hypopituitarism may be treated with subcutaneous infusions of FSH, human chorionic gonadotropin (hCG), which mimics the action of LH, and occasionally GnRH. Growth hormone replacement therapy seems to play an important role in sensibilization of ovary responsivity, follicular growth and uterine morphology in those growth hormone deficiency patients. In pregnant women, growth hormone replacement is not recommended.

It is unlikely that patients will ever return to normal pituitary function and will therefore be on lifelong hormone replacement. It is therefore important that they will be followed up by an endocrinologist.

**Surgical therapy**

If the cause of hypopituitarism is tumor, it must be removed by:

**Transsphenoidal surgery**

Transsphenoidal surgery is a removal of the tumor by an operation through the nose and the sphenoidal sinuses. It may, apart from addressing symptoms related to the tumor, also improve pituitary function, although the gland is sometimes damaged further as a result of the surgery.

**Craniotomy**

Craniotomy is a procedure of opening the skull. The recovery is less likely, but sometimes this is the only suitable way to approach the tumor.

After surgery, it may take some time for hormone levels to change significantly. Retesting the pituitary hormone levels is therefore performed 2 to 3 months later.

**Assisted reproduction**

If conservative medical treatments fail to achieve a full term pregnancy, the physician may suggest the patient undergo in vitro fertilization (IVF). IVF and ART generally start with stimulating the ovaries to
increase egg production. Most fertility medications are agents that stimulate the development of follicles in the ovary. Hormone replacement therapy is used before ART treatment to improve follicular growth and the success rate of pregnancy and those patients need higher doses for stimulating the process as compared with other causes of anovulation. The treatment consists of ovulation induction by administrating of gonadotropins. If it doesn’t work, the hormone replacement therapy consists of combination with growth hormone and then ovulation induction began.

After stimulation, the physician surgically extracts one or more eggs from the ovary, and unites them with sperm in a laboratory setting, with the intent of producing one or more embryos. Fertilization takes place outside the body, and the fertilized egg is reinserted into the woman's reproductive tract, in a procedure called embryo transfer.

Approximately 14 days after the embryo transfer the woman should have a quantitative beta hCG (human chorionic gonadotropin). This is the first measurable indication of embryo implantation.

### Find more about related issues

#### Organs

**Hypothalamus**
A region of the forebrain that regulates body temperature, some metabolic processes and governs the autonomic nervous system.
Learn more at: [www.fertilitypedia.org/edu/organs/hypothalamus](http://www.fertilitypedia.org/edu/organs/hypothalamus)

**Pituitary gland**
An endocrine gland, about the size of a pea, whose secretions control the other endocrine glands and influence growth, metabolism, and maturation.
Learn more at: [www.fertilitypedia.org/edu/organs/pituitary-gland](http://www.fertilitypedia.org/edu/organs/pituitary-gland)

#### Risk factors

**Low level of FSH**
A condition with low serum follicle-stimulating hormone (FSH) concentration.
Learn more at: [www.fertilitypedia.org/therapy/rf/low-level-of-fsh](http://www.fertilitypedia.org/therapy/rf/low-level-of-fsh)
Low level of LH
A serum luteinizing hormone (LH) levels under normal serum concentration for gender and age. Learn more at: www.fertilitypedia.org/therapy/rf/low-level-of-lh

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

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

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

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