Reduced function of adrenal glands which may cause impaired fertility in both genders.

About Adrenal insufficiency

Adrenal insufficiency (AI) is a condition in which the adrenal glands do not produce adequate amounts of steroid hormones. These include primarily cortisol, but may also include impaired production of aldosterone (a mineralocorticoid). AI develops only when a large part of the function of the adrenal gland is lost. Congenital adrenal hyperplasia (CAH) is the most common type of adrenal insufficiency, it is a genetic disorder causing the malfunction of adrenal cortex.

The adrenal gland is made of two functional units (Pic. 1), the medulla which produces catecholamines and cortex composed of three zones: zone glomerulosa, superficially located, producing mineralocorticoids (aldosterone and corticosterone), zone reticularis deeper sited producing weak androgens and zone fasciculate producing corticosteroids (cortisol and corticosteron).

Aldosterone is the main mineralocorticoid hormone. It is essential for sodium conservation in the kidney, salivary glands, sweat glands and colon. It plays a central role in the regulation of the plasma sodium (Na⁺), the extracellular potassium (K⁺) and arterial blood pressure. When dysregulated, aldosterone is pathogenic and contributes to the development and progression of cardiovascular and renal disease.

Cortisol is the main corticosteroid derived from cholesterol. Cortisol circulates in plasma either in its free and active form or in its inactive form, reversibly...
bound to proteins. It is released in response to stress and low blood-glucose concentration. It increases blood sugar to suppress the immune system and to aid in the metabolism of fat, protein, and carbohydrates.

Production of corticosteroids is regulated by the hypothalamic–pituitary-adrenal (HPA) axis. Cortisol production and secretion is stimulated mainly by the adrenocorticotrophic hormone (ACTH). This is a peptide produced in the anterior pituitary. In the short term, ACTH stimulates cortisol production and secretion even if cortisol storage in adrenal glands being low; in the longer term, ACTH also stimulates the synthesis of enzymes that are involved in cortisol production, as well as their cofactors and adrenal receptors for cholesterol. ACTH also stimulates the production of adrenal androgens and, to a lesser extent, mineralocorticoids.

Depending on the origin of adrenal insufficiency, it is defined as **primary** or **secondary**:

**Primary adrenal insufficiency**

Autoimmune and tuberculous adrenalitis (adrenal infection) are the principal aetiologies for primary adrenal failure, which is characterized by low cortisol levels and elevated plasma concentrations of ACTH. Primary AI is caused by processes that damage the adrenal glands. Infection diseases, viral and fungal especially, may cause chronic primary AI, particularly in immunosuppressed patients, like HIV patients.

**Secondary adrenal insufficiency**

Impairment of the hypothalamic-pituitary corticotropic axis is responsible for secondary causes of adrenal insufficiency. These situations are characterized by low circulating levels of cortisol and ACTH. The most frequent cause of secondary adrenal insufficiency is a tumour of the hypothalamic-pituitary region but administration of supraphysiologic doses of glucocorticoids may alter a normal hypothalamic response with secondary adrenal failure once individuals are weaned from the glucocorticoid treatment. Bilateral adrenalectomy (surgical removal of adrenal gland) or drug-induced adrenal insufficiency may be considered as iatrogenic aetiologies for adrenal failure.

Evaluating adrenal function is a difficult task in clinical practice. Conversely, the high dose ACTH-stimulation test is generally accepted as reliable to evaluate adrenal function in everyday practice, and considered as the easiest to perform. Lab test to be run should also include: random cortisol, serum ACTH, aldosterone, renin, potassium and sodium. A CT (computer tomography) of the adrenal glands can be used to check for structural abnormalities of the adrenal glands. An MRI (magnetic resonance imaging) of
the pituitary can be used to check for structural abnormalities of the pituitary.

The treatment of adrenal insufficiency usually involves administration of medications altering the adrenal function. The type of medication varies depending on whether cortisol production or aldosterone production is impaired. In case of adrenal crisis, the treatment involves the application of intravenous fluids and steroids as it is life threatening situation.

**Symptoms**

Symptoms commonly associated with adrenal insufficiency are **fatigue** (lack of energy or stamina), **abdominal pain, nausea**, and **dizziness** (hypotension symptoms). Signs associated with adrenal insufficiency are **low blood pressure**, **vitiligo** (loss of pigmentation cells in the skin) and/or **skin changes**. Biological markers of the disease include hyperkalaemia (elevated potassium concentrations in blood), hyponatremia (low sodium concentration in blood), acidosis (increased acidity of blood), hypercalcaemia (elevated calcium concentrations in blood) and eosinophilia (increased concentration of specific leukocytes in peripheral blood).

**Associated diseases**

- Addison's disease (long term endocrine disorder of adrenal gland)
- β-thalassemias (a group of hereditary blood disorders)
- Lung cancer
- Pituitary cancer
- Waterhouse-Friderichsen syndrome (adrenal gland failure due to bleeding into the adrenal glands caused by infection)
- Smith–Lemli–Opitz syndrome (genetically predisposed disorder of cholesterol metabolism)
- Bassen-Kornzweig syndrome (genetically predisposed disorder interfering with the normal absorption of fat and fat-soluble vitamins)

**Complications**

**Critical illness-related corticosteroid insufficiency (CIRCI)**

It is a form of adrenal insufficiency in critically ill patients who have blood corticosteroid levels which are inadequate for the severe stress response they experience. Combined with decreased glucocorticoid receptor sensitivity and tissue response to corticosteroids, this adrenal insufficiency constitutes a negative prognostic factor for intensive care patients.

**Adrenal crisis (Addisonian crisis and acute adrenal insufficiency)**

It is a medical emergency and potentially life-threatening situation requiring
immediate emergency treatment. It is a constellation of symptoms that indicate severe adrenal insufficiency caused by insufficient levels of the hormone cortisol. This may be the result of either previously undiagnosed or untreated Addison's disease, a disease process suddenly affecting adrenal function (such as bleeding from the adrenal glands in Waterhouse-Friderichsen syndrome), suddenly stopping intake of glucocorticoids, or an intercurrent problem (e.g. infection, trauma, in fact any form of physical or mental stress).

**Risk factors:**

- genetic predispositions
- viral and fungal infections
- high dosages of glucocorticoids

**Prevention**

Regarding the genetically predisposed adrenal conditions, there is no way to prevent the development. In case of AI induced by administration of glucocorticoid, the only way to prevent its development is by restraining the application of high dosage of glucocorticoids if possible. AI may be also caused by infections, in such cases the best way to prevent its development is to maintain high hygiene standards. As the AI may be a result of metastatic spreading of cancer, the healthy lifestyle is also recommendable to decrease the chances of cancer development in first place.

### How it can affect fertility

**Congenital adrenal hyperplasia**

Irregular menses are common in females with CAH. The number of pregnancies among women with CAH is related to the severity of the mutation. Reports in women with classical CAH suggest that elevated progesterone concentrations play an important role in preventing menstrual cyclicity and fecundity.

**Non-Classical Congenital Adrenal Hyperplasia (NCAH)**

Women with Non-Classical Congenital Adrenal Hyperplasia (NCAH) often present reduced fertility due to secondary PCOS and hyperandrogenism (elevated concentrations of male sex hormones), which inhibit the normal hormonal cycle resulting in anovulation. Persistently elevated levels of progesterone during the follicular phase (oocyte and follicle development) in women with NCAH may interfere with the quality of cervical mucus (protective
substances located in the cervi of the uterus), preventing sperm penetration. In addition, elevated levels of progesterone (female sex hormone) during the preovulatory (follicular) phase of the menstrual cycle may result in inadequate endometrial maturation (maturation of the inner layer of the uterus) and impaired embryo implantation (“nesting” of an egg into the uterine wall).

**Addison’s disease**

It is characterized by deficiency of cortisol, aldosterone and androgen hormonal precursors, usually caused by an autoimmune reaction towards the adrenal cortex. The loss of adrenal androgens could possibly influence fertility and increase in spontaneous abortions and has been associated with Addison’s disease present in pregnancy, but the prognosis of pregnancies in patients with known Addison’s disease has usually been considered good. Concomitant diseases, such as autoimmune thyroid disease and premature ovarian insufficiency (POI; preterm cessation of ovarian function) are possible causes of reduced fertility in these patients, as well as inappropriate treatment of adrenal insufficiency and the burden of disease, with loss of energy and vitality required for wanting and planning a pregnancy and to rear children.

**Stress conditions**

Excess stress raises cortisol levels and drops progesterone levels (both potential signs of infertility). The adrenals produce progesterone before converting it into cortisol. If the adrenals are exhausted, they will rob other sources of progesterone, notably ovarian. This impacts on the reproductive cycle. Stress can cause anovulation and miscarriages. Patient suffering from AI is at increased risk of experiencing those symptoms due to stress conditions.

**Male infertility**

Increased levels of cortisol may lead to altered sperm production resulting in decreased sperm motility and concentration. Yet men’s fertility is usually less affected by AI than women’s fertility potential.

**Prognosis**

It is certain that AI can interfere with fertility potential. The early diagnosis of AI has utmost importance not only for prevention of serious health complications but also for effective management of the disease decreasing the impact on general quality of life. With proper medication, the management of AI raises the fertility potential in both, women and men. The treatment is especially
significant in women, as there is a larger variety of AI effects on reproductive function. Depending on the cause of AI it is recommendable to perform genetic test on the early developed offspring in order to increase the chances of early diagnosis of AI.

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