

# Menstrual Cycle Disturbances at Reproductive Age

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## 1. Introduction

During the last decade, the rapidly expanding fields of molecular biology and genetics have allowed us to better understand the clinical symptoms of endocrine disorders, including menstrual cycle disturbances at reproductive age. This chapter is an attempt to combine the results of new research and hypotheses with the proven facts about disorders of the functioning of the hypothalamic-pituitary-ovary axis.

## 2. Menstrual cycle

The menstrual cycle, as defined in the introduction, is the complex of changes which are the result of functional integration of stimulatory and inhibitory signals from the hypothalamus, pituitary and ovary. At the reproductive age, from puberty to menopause, normal function in women involves repetitive cycles of follicle development, and ovulation. The average menstrual cycle is 28 days from the start of one to the start of the next, but it can range from 21 days to 35 days. The menstrual cycle is divided into three phases: the follicular phase (postmenstrual), ovulation, and the luteal phase (premenstrual). Menstrual cycles are counted from the first day of menstrual bleeding. The length of the follicular phase depends on the rate of growth of the ovarian follicles and is thus variable from one woman to another. In contrast, the length of the luteal phase depends on the life span of the corpus luteum (CL), and is thus less variable. The mean duration of the follicular phase is  $15.4 + 2.5$  days and the mean duration of the luteal phase is  $13.6 + 1.2$  days. The early follicular phase starts on the first day of the cycle and ends when estradiol begins to increase. It is characterized by increasing LH and FSH and constant low levels of estradiol. The late follicular phase starts with the increase in estradiol and ends at its preovulatory peak. It is characterized by increasing estradiol and decreasing FSH levels.

The average level of estradiol ranges from 48 pg/ml in the early follicular phase, up to 168 pg/ml in the late follicular phase. At the peak, the level can reach 250 pg/ml. The average LH level ranges from 3 IU/l in the early follicular phase up to 4,5 IU/l in the late follicular phase, with ovulation peak to 12 IU/ml. The average level of FSH ranges from 6 IU/l in the early follicular phase up to 4 IU/l in the late follicular phase.

Ovulation occurs about 36 h after the LH peak, which is preceded by the estradiol peak. The early luteal phase starts on the day of ovulation (the day after the LH peak) and ends when progesterone has reached a plateau. It is characterized by increasing progesterone and

decreasing LH and FSH levels. The mid-luteal phase corresponds to plateauing progesterone levels. It is characterized by constant elevated progesterone and constant low levels of LH and FSH. The late luteal phase starts when progesterone decreases and ends on the day preceding the next menses. It is characterized by decreasing progesterone and increasing LH and FSH levels. The average estradiol level in the mid-luteal phase is about 250 pg/l, and average progesterone level at the same time is 12 ng/ml.

### 3. Hypogonadotropic hypogonadism

Hypogonadotropic hypogonadism (HH) is characterized by absent or decreased function of the male testes or the female ovaries. It can be defined by inappropriately low serum concentrations of LH and FSH, which is an effect of GnRH deficiency. HH is most frequently acquired and caused by a number of pathological processes but it can also occur as part of various congenital syndromes. The terminology of HH has evolved with the increased understanding of reproductive physiology. Once functional and later genetic causes of central hypogonadism were identified, "idiopathic" or "isolated" HH (IHH) was then used to indicate cases in which secondary causes of HH had been excluded. Acquired and syndromic causes of HH include the following: CNS or pituitary tumors, brain/pituitary radiation, pituitary apoplexy, head trauma, drugs (GnRH agonists/antagonists, glucocorticoids, narcotics, chemotherapy), functional deficiency resulting from chronic systemic illness, eating disorders, hypothyroidism, hyperprolactinemia, diabetes mellitus, and Cushing's disease. Most of the above causes of HH will not be discussed because they do not fall within the scope of the chapter.

Idiopathic hypogonadotropic hypogonadism (IHH), also called isolated GnRH deficiency, is characterized by a failure of initiation of puberty due to insufficient gonadotropin release, thus resulting in the failure to develop secondary sexual characteristics and a mature reproductive system. Currently known genetic defects account for about 30% of all IHH cases. When embryonic migration of GnRH neurons from the nasal placode to their final destination in the hypothalamus is disrupted, the resulting phenotype is Kallmann syndrome, which is clinically characterized by hypogonadotropic hypogonadism and anosmia. Normosmic idiopathic hypogonadotropic hypogonadism (nIHH) resulting from Kallmann syndrome has been observed. Family members with the same genotype may display a range of features of the GnRH neurons that successfully completed their embryonic journey to the hypothalamus. The prevalence of IHH has been estimated at 1/4000 to 1/10 000 in males. It is reported to be between 2 and 5 times less frequent in females (Brioude, 2009).

The classification of IHH has recently been made on the basis of genetic and pathophysiological features. Now a division into two forms of IHH been proposed. The paradigm of this division is to define Kallmann syndrome as a form generally combined with anosmia. There is substantial variation in clinical expression of the same genetic defect in families of patients with complete anosmia and hypogonadotropic hypogonadism to less severe hypogonadotropic hypogonadism manifesting as delayed puberty.

#### 3.1 Genetic basis for IHH

The genetic causes of Kallmann syndrome and nIHH are summarized in Table 1. Some genes (FGFR1, FGF8, PROKR2, PROK2, CHD7) have been associated with both Kallmann syndrome and nIHH.

Gene	Year linked to human HH	Syndrome name	Phenotypes	Inheritance	Comment
<i>KAL1</i>	1991	Kallmann Syndrome 1	KS	X-linked R	70% synkinesia 30% unilateral renal agenesis
<i>FGFR1</i>	2003	Kallmann Syndrome 2	KS nIHH	DA (AR) oligogenic	30% Cleft lip/palate common
<i>PROKR2</i>	2006	Kallmann Syndrome 3	KS nIHH	AR AD oligogenic	Weak reported association with epilepsy, sleep disorder, synkinesia, fibrous dysplasia, obesity
<i>PROK2</i>	2006	Kallmann Syndrome 4	KS nIHH	AR AD oligogenic	synkinesia, fibrous dysplasia, obesity
<i>CHD7</i>	2004	Kallmann Syndrome 5	CHARGE syn KS	AD	Deafness and semicircular canal hypoplasia common
<i>FGF8</i>	2008	Kallmann Syndrome 6	KS nIHH	AD (AR) oligogenic	Cleft lip/palate relatively common
<i>GNRHR</i>	1997		nIHH	AR oligogenic	No accessory features
<i>GNRH1</i>	2009		nIHH	AR AD?	No accessory features
<i>KISS1R</i>	2003		nIHH	AR	No accessory features
<i>TAC3</i>	2009		nIHH	AR	Only 2 patients described to date, both with mild learning disability
<i>TACR3</i>	2009		nIHH	AR	No accessory features

KS, Kallmann syndrome; nIHH, normosmic isolated hypogonadotropic hypogonadism; AD, autosomal dominant; AR, autosomal recessive.

Table 1. Genetic defects causing idiopathic hypogonadotropic hypogonadism (IHH) (modified by Semple and Topaloglu 2010 )

Kallmann syndrome 1, caused by mutation in the *KAL1* gene, is inherited in an X-linked manner. Deletion of *KAL1* is an extremely rare cause of this syndrome. The *KAL1* gene encodes an extracellular glycoprotein called anosmin-1, which is an adhesion molecule responsible for the migration of GnRH neurons and formation of the olfactory bulb in the fetal period. The syndrome has not been described in women so far.

*Kallmann syndrome 2 and 6* are caused by mutations of the *FGFR1* (fibroblast growth factor receptor) and *FGF8* (fibroblast growth factor 8) genes. *FGFR1* requires heparin sulfate proteoglycans as co-receptors, and anosmin-1. Loss of *FGFR1* function has been confirmed to produce reproductive abnormalities ranging from severe autosomal dominant Kallmann syndrome through autosomal dominant, fully penetrant nIHH to delayed puberty. Approximately 10% of patients with Kallmann syndrome were found to have loss of function mutations in *FGFR1*. *FGF8* mutation patients exhibited various degrees of olfactory

function and GnRH function. In addition, cleft palate is found in up to 30% of patients, while cartilage abnormalities in either ear or nose and some digital anomalies have been reported (Tsai & Gill, 2006).

*Kallmann syndrome 3 and 4* are caused by mutations in the PROKR2 (prokineticin receptor 2) and PROK2 (prokineticin 2) genes. Prokineticin 2 is an 81-amino acid peptide, which together with its receptor was recognized as a strong candidate for failed development of the olfactory bulb and migration of GnRH neurons. These syndromes were found in 9% of Kallmann syndrome patients, most of them being heterozygous; however, homozygous and compound heterozygous mutations were also described. Patients with PROK2 or PROKR2 mutations have considerable phenotypic variability ranging from Kallmann syndrome to nIHH. A variety of accompanying clinical features including fibrous dysplasia, synkinesia, and epilepsy have been reported in patients with PROK2 or PROKR2 mutations.

*Kallmann syndrome 5* is caused by a mutation of the CHD7 gene, which encodes a chromatin-remodeling factor (chromodomain helicase DNA-binding protein 7) and is defective in CHARGE syndrome. Some patients also have IHH and hyposmia. On the basis of the hypothesis that Kallmann syndrome and nIHH may be a milder allelic variant of *CHARGE syndrome*, patients diagnosed with hypogonadotropic hypogonadism and anosmia should be screened for clinical features consistent with CHARGE syndrome.

The term “CHARGE syndrome” is used to describe a pattern of birth defects in children with coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital anomaly and ear abnormality. The prevalence of CHARGE syndrome is approximately 1 in 10 000, and more than 400 patients have now been reported (Aminzadeh et al., 2010). The clinical criteria of CHARGE syndrome are summarized in Table 2.

*GnRH and GnRHR gene defects* cause nIHH. To date, many familial and some sporadic cases of GnRHR gene mutation have been reported. On the basis of a large series GnRHR mutations have been suggested to account for about 40–50% of familial nIHH, and around 17% of sporadic nIHH. In most early reports, the GnRHR defects consisted of point mutations leading to amino acid substitutions. Rarer mutations lead to frame-shifts or premature stop codons, resulting in a truncated protein, but no true GnRHR deletions have so far been described (Bouligand et al., 2009). The most consistent characteristic of patients with GnRHR mutation is their pituitary resistance to pulsatile GnRH administration when the phenotype is severe. Pregnancy has been obtained after pulsatile administration of GnRH. In addition, isolated cases of nIHH have presented with pregnancy after clomifene citrate administration (Brioude et al., 2009). The differentiated clinical expression of GnRHR mutation results in partial loss of the GnRHR function, and in one case this was attributed to interaction with a mutation in FGFR1, which produces different phenotypes (Pitteloud, 2007).

Recently, defects in the GNRH1 gene itself were reported for the first time. Chan et al. (2009) reported a homozygous mutation in a male patient with severe nIHH. This single base-pair deletion produces a frame shift that is predicted to disrupt the GnRH decapeptide. These authors also identified a rare heterozygous GnRH1 sequence variant in four patients with nIHH. Simultaneously, Bouligand et al. (2009) presented isolated familial nIHH and GnRH1 mutation. The case reports concerned two of four children of non-consanguineous parents who were found to have nIHH. Both the brother and his sister showed characteristics of severe nIHH, and simultaneously they had a blunted response to GnRH bolus administration (100 µg intravenously).

Major criteria	Minor criteria	Inclusion rule
Coloboma of the iris, retina, choroid or disc (75-90%)  Microphthalmia	Hypoplastic genitalia - micropenis and cryptorchidism (80%) - hypoplastic labia (30-40%)  HH (65-85%)	4 majors OR 3 majors + 3 minors
Choanal atresia (35-65%)	Developmental delay - delayed motor milestones - language delay - learning disability of varying degree	
Ear abnormalities (>95%) - external ear (lop or cup shaped) - middle ear (ossicular malformations; chronic serous otitis media) - inner ear (cochlear defects) - mixed deafness (60-90%)	Cardiovascular malformations - conotruncal defect, e.g. Fallot's tetralogy - AV canal defects - aortic valve or arch defects	
Cranial nerve dysfunction - unilateral or bilateral facial palsy - sensorineural deafness - swallowing problems	Growth deficiency - short stature - GH deficiency Orofacial cleft (15-20%) Tracheoesophageal fistula Characteristic facies	

Table 2. Clinical criteria of CHARGE Syndrome by Aminzadeh et al. (2010)

In 2003 there was described a mutation in the G-protein-coupled receptor *GPR 54* (de Roux, 2003). *GPR 54* had previously been shown to be the receptor for a small peptide derived from the *KISS1* gene (leading to its recent redesignation as *KISS1R*). Before this discovery, some cases of familial nIHH had been identified as resulting from defects of the short arm of chromosome 19 (Seminara et al., 2003). Two genetic studies performed in the USA and in France demonstrated that nIHH may be due to inactivation of *KISS1R* (Iovane, 2004). *KISS1R* mutations are a rare cause of nIHH. Individuals with nIHH have been shown to have severely reduced LH pulse amplitude, but approximately normal pulse frequency. Successful pregnancy has been reported after specific stimulation of ovulation (Semple & Topaloglu, 2010).

Topaloglu et al. (2009) reported four human pedigrees with severe congenital gonadotropin deficiency and pubertal failure in which all affected individuals are homozygous for loss of function mutation in *TAC3* (encoding neurokinin B) or its receptor *TACR3* (encoding neurokinin B receptor). Gianetti et al. (2010) presented phenotypic information concerning seven females with coding sequence variants in *TACR3/TAC3*. None of the females had spontaneous thelarche, and five of them demonstrated evidence for reversibility of their hypogonadism after discontinuation of therapy. Neurokinin B, a member of the substance P related tachykinin family, is known to be highly expressed in hypothalamic neurons,

especially in the actuate nucleus, and is co-expressed there with kisspeptin. Neurokinin B exerts an influence on reproductive function, but its importance in sustaining the integrity of the hypothalamic-pituitary-gonadal axis is expected to be elucidated over the next few years.

### 3.2 Clinical presentation

Kallmann syndrome may be suspected in a prepubertal patient with anosmia, especially when there is already a positive family history. Usually, however, a clear picture of the disorder is revealed in adolescence. Rarely, individuals have normal sexual maturation and develop IHH in adulthood. The majority of girls can be suspected of IHH when pubertal development is incomplete or absent after the age of 13 years. Primary amenorrhea occurs in approximately 90% of cases of IHH. Girls before puberty have normal growth of stature, but the pubertal growth spurt does not occur. Stature retardation is very rare, but in contrast the absence of long-bone epiphyseal closure explains these patients' frequent eunuchoid aspect and relative tallness. To distinguish nIHH from constitutional late puberty could be difficult when these reversible forms occur before 20 years of age.

Adult females have little or no breast development, although in some patients it may be almost normal. Since adrenal maturation proceeds normally, the low levels of androgen production in the adrenal glands may allow normal onset of pubic hair growth (adrenarche) and therefore the pubic hair may be absent, sparse, or even normal. Partial forms are frequent in women, while very mild form occurs in only a minority of women. This form of IHH can be revealed by isolated chronic anovulation, whereas estradiol secretion is adequate for endometrial development, and can be shown by onset of bleeding after progestin administration, as well as by oligomenorrhea. These attenuated forms have also been described as having conceived spontaneously.

Retarded bone maturation, osteopenia and osteoporosis are frequent when the gonadotropin deficiency is discovered in adulthood (Brioude, 2009).

### 3.3 Establishing the diagnosis

The diagnosis of IHH is established by the presence of both suggestive clinical findings and laboratory findings consistent with hypogonadotropic hypogonadism, and the absence of secondary causes of hypothalamic hypogonadism. The first step of the diagnostic procedure is a detailed physical examination with the assessment of development of the secondary sexual characteristics, and checking family history. Then it is necessary to perform a semi-quantitative assessment of olfaction to detect hyposmia. Examination of the outer ear and hearing is also useful to rule out mild CHARGE syndrome. In women without anosmia or hyposmia or identified genetic anomalies, the diagnostic procedure should exclude eating disorders, excessive physical activity, and chronic underlying conditions. Body mass index and body fat should also be calculated. Laboratory tests should be limited to assessing the level of LH, FSH, PRL and estradiol. Plasma LH, FSH and estradiol concentrations are often low in women, sometimes being near the detection limit. In very mild form, which occurs in only a minority of women, nIHH can be revealed by isolated chronic anovulation, whereas estradiol secretion is almost normal. The test with intravenous administration of 100 µg GnRH provides no extra diagnostic information relative to baseline gonadotropic levels, but its outcome reflects the severity of the gonadotropin deficiency

The diagnostic procedures should also exclude hyperprolactinemia, global anterior pituitary insufficiency and an associated endocrine disorder that may be part of syndromic forms of IHH.

Magnetic resonance imaging (MRI) of the brain and olfactory bulbs is useful in IHH. MRI can rule out expansive, infiltrative, or malformative disorders, and can also be useful to analyze the olfactory bulbs. Renal ultrasound examination should be made in Kallmann syndrome, as it can reveal renal malformation or agenesis. Pelvic sonography, which is now a routine part of gynecological examination, should always be performed to determine the size of the uterus, endometrial thickness and ovary development. In adult women, especially those with osteoporotic risk factors, such as glucocorticoid treatment and smoking, one should consider measuring bone mineral density.

### 3.4 Management

Treatment options for IHH include sex steroid, gonadotropins, and pulsatile GnRH administration. The choice of therapy is determined by the goal of treatment. The majority of young women have a lack of development of the secondary sexual characteristics, and they should be treated with estrogens, initially with low doses (1 mg/estradiol p.o.). After a period of approximately six months when breast development has been optimized, replacement doses of estradiol and progestagens should be implemented. In women with nIHH who wish to become pregnant pulsatile GnRH stimulation can be used. Intravenous pulsatile administration of GnRH mimics normal cycle dynamics with the resulting ovulation of a single follicle (Layendecker et al., 1980). This therapy offers a clear advantage over treatment with exogenous gonadotropins, which involves higher rates of both multiple gestation and ovarian hyperstimulation syndrome. For either approach, however, the rate of conception is approximately 30% per ovulation cycle (Brioude, 2009). Recently, in nIHH women in order to stimulate ovulation recombinant FSH is commonly used. Its use provides a low risk of hyperstimulation syndrome. But in the cases of severe form of IHH at a concentration of LH in the blood below 1.2 mIU/ml, it is necessary to add to the therapy recombinant hCG, or a preparation containing FSH and LH, or recombinant LH, since FSH administration itself does not lead to luteinization of granulosa cells. It is also recommended to follow it with administration of progesterone to maintain corpus luteum function. This therapeutic regimen is assessed to give 70% of pregnancies with the application of 6 cycles of treatment, but it increases the risk of ovarian hyperstimulation syndrome and the development of multiple pregnancies.

## 4. Nutritional hypothalamic dysfunction

Adaptation of a woman's body to starvation leads to menstrual and fertility disorders. A number of reproductive disorders have emerged that appear to be related to dieting and the desire for leanness. Adolescent girls who present with eating disorders before menarche have not only lost weight but are also stunted in growth (Swenne & Thurfjell, 2003). Girls first begin to develop a preoccupation with dieting for weight loss and to describe feelings and behaviors associated with dieting around the time of menarche. This concern is accentuated by the rapid increase in height, weight, and body fat that occurs just before menarche, but it is also related to a window of vulnerability to sociocultural influences that focus on body image and weight. Most eating disorders first develop in

adolescence, with 90% of eating disorders present before age 25 (Andersen & Ryan, 2009). In healthy adult women, a short-term calorie restriction diet (800 – 1100 kcal/per day) does not change the menstrual rhythm. When dietary restriction persists for more than one cycle, it is followed by weight loss and suppression of ovulation. Moderate dietary restriction and weight loss in normal cyclic women are associated with a reduction of estradiol levels in the face of almost normal LH levels,  $\alpha$  consequence of which is *functional hypothalamic amenorrhea (FHA)*. Severe starvation in healthy women for two and half weeks induces a reversal of LH pulses to prepubertal patterns (Yen, 1999). Women with FHA have reduced central GnRH drive, resulting in low FSH and LH levels, which causes anovulation.

The most serious eating disorders, such as anorexia nervosa, bulimia nervosa, and binge eating disorder, were recently classified as psychiatric illnesses, and therefore will not be discussed in this chapter.

## 5. Athletic amenorrhea

The physiological and psychosocial health benefits of exercise have been widely promoted by society, but we should not forget that intense exercise can cause adverse health effects. First described in 1997, the *female athletic triad* is a syndrome that includes disordered eating, amenorrhea and osteoporosis. Athletic amenorrhea has been described in women involved in long-distance running, rowing, skiing, high-performance gymnastics, volleyball, judo and ballet. It was found that the disorder may affect not only professional sportswomen, but also women practicing recreational exercises. Intense recreational exercises cause 1/3 of these women to develop ovulatory dysfunction. Female athletes are characterized by changes in metabolism in the form of intermittent or chronic imbalance due to increased energy expenditure or caloric intake. Another factor negatively affecting hypothalamic function is stress associated with competition and performances. Under normal conditions, after acute stress or energy demand passes, hormonal equilibrium is restored. In contrast, chronic stress can result in alteration of hormone secretion, and in particular it may damage hypothalamic secretory function. The important role played by energy imbalance and psychological factors in the pathogenesis of athletic amenorrhea should be stressed (Pauli & Berga, 2010).

Risk factors of athletic amenorrhea are age below 17 years, psychological factors and food restrictions. But the mechanism most likely to initiate development of the disorder is a disparity between the calorie intake and energy expenditure. FHA is estimated to affect up to 5% of women of reproductive age and is the underlying cause of 35% of women seeking evaluation for secondary amenorrhea.

This disorder of energy balance reduces the activity of the hypothalamic centers responsible for the secretion of GnRH. Reduction of central drive GnRH results in low FSH and LH levels, which causes anovulation. In FHA women the disruption of GnRH drive is also connected with activation of the hypothalamic-pituitary-adrenal (HPA) axis, and suppression of the hypothalamic-pituitary-thyroidal (HPT) axis. Changing functions of the two axes is due to the need to mobilize energy in response to stress. Other peripheral metabolic factors such as ghrelin, insulin, leptin and peptide YY also play a role in communicating energy status to the brain areas that modulate metabolism. Gut peptides and adipocytokines also appear to be altered in exercising women with FHA, and have been hypothesized to be involved in the etiology of this disorder. Ghrelin is produced by cells in

the stomach and appears to be a signal of disordered eating independent of weight or body fat, such that elevated ghrelin may result in continuing suppression of the hypothalamic-pituitary-ovarian axis with amenorrhea despite normal body fat and leptin levels. Eating disorders are also characterized by elevations in corticotropin-releasing hormone and cortisol, along with loss of the normal circadian rhythm of cortisol. Neuropeptide Y is produced by nuclei in the hypothalamus and appears to have both stimulatory and inhibitory effects on GnRH secretion in response to leptin (Andersen, et al., 2009). A critical leptin level threshold is suggested to be necessary for regular menses. Additionally, in FHA elevated night time serum growth hormone levels and lower 24 h prolactin levels have been observed (Berga et al., 1989).

The prospective study of Rauh et al. (2010) showed that high school female athletes with disordered eating and oligomenorrhea/amenorrhea have a reduced BMD (bone mineral density). A BMD level below the expected range for age was associated with musculoskeletal injury. The authors conclude that BMD levels should begin to be closely monitored in adolescent female athletes.

## 6. Eating disorders and athletic amenorrhea treatment

Appropriate intervention depends on determining which behavior needs to be modified. Attention should be concentrated on the promotion of psychosocial harmony, restoring ovulation and menstrual cyclicality. Methods that are considered useful include a combination of cognitive behavior therapy with relaxation techniques coupled with adequate caloric intake. One should avoid extensive workups for physical causes when women have a clear fear of fatness, drive for thinness, preoccupation with weight, bingeing and purging, or compulsive exercise suggesting an eating disorder. The implementation of hormonal therapy to regularize menstrual cycles is not indicated when the patient is underweight, dieting despite normal weight range, or compulsively exercising. It is advisable to prescribe 1500 mg calcium citrate/400 units vitamin D per day in divided doses. Before the plan of ovulation stimulation in order to become pregnant, a healthy weight should be established. The patient should also be educated about the effect of underweight on ovulation and risks of eating disorders for pregnancy and offspring (Andersen, et al., 2009).

## 7. Hypopituitarism

Hypopituitarism is defined as a clinical syndrome of deficiency in pituitary hormone production. This may result from disorders involving the pituitary gland, hypothalamus, or surrounding structures. Panhypopituitarism refers to involvement of all pituitary hormones; however, only one or some pituitary hormones are often involved, resulting in partial hypopituitarism. The Regal et al. (2001) population-based study noted an incidence of hypopituitarism of 4.2 cases per 100 000 per year, increasing with age. It should be noted that the study involved an adult Caucasian population of northwestern Spain.

Pituitary hormones of clinical significance include adrenocorticotrophic hormone (ACTH, i.e., corticotropin), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), prolactin (PRL), thyroid-stimulating hormone (TSH, i.e., thyrotropin), and antidiuretic hormone (ADH) (Fig. 1 ). Presented symptoms of the disease depend on the specific pituitary hormone deficiency, as summarized in Table 3.

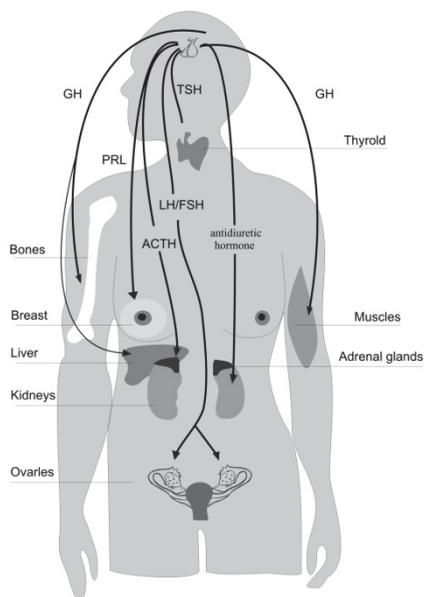


Fig. 1. Function of pituitary hormones.

Deficient hormone	Symptoms
GH	Growth retardation in children. Adults: excessive tiredness, muscle weakness, lack of drive, impaired quality of life scores
FSH/LH (women)	Amenorrhea, reduced libido, dyspareunia, and hot flashes
TSH	Weight gain, decreased energy, sensitive to cold, constipation, dry skin
ACTH	Pale appearance, weight loss, low blood pressure, dizziness, tiredness
AVP	Thirst, polyuria and nocturia – diabetes insipidus (pituitary adenomas themselves rarely cause diabetes insipidus unless it occurs after surgery. If it occurs spontaneously, usually some other sort of tumor or inflammation is present in the area)
PRL	The mother might not be able to breast feed following delivery.

Table 3. Symptoms of pituitary hormone deficiency (modification by The Pituitary Foundation 2010)

There are numerous causes of hypopituitarism (Table 4).

Traumatic brain injury (TBI) and subarachnoid hemorrhage have long been known to cause lesions in the hypothalamo-pituitary region. Therefore, it is considered that TBI is one of the main causes of hypopituitarism. TBI is also the main cause of death and disability in young

Brain damage*	Traumatic brain injury Subarachnoid hemorrhage Neurosurgery Irradiation Stroke
Pituitary tumors*	Adenomas Other
Non-pituitary tumors	Craniopharyngiomas Meningiomas Gliomas Chordomas Ependymomas Metastases
Infections	Abscess Hypophysitis Encephalitis
Infarction	Apoplexy Sheehan's syndrome
Autoimmune disorders	Lymphatic hypophysitis
Haemochromatosis, granulomatous diseases, histiocytosis Empty sella Perinatal insults Pituitary hypoplasia or aplasia Genetic causes Idiopathic causes	

\*Pituitary tumors are classically the most common cause of hypopituitarism. However, new findings imply that causes related to brain damage might outnumber pituitary adenomas in causing hypopituitarism.

Table 4. Causes of hypopituitarism (by Schneider et al. 2007)

adults, with consequences ranging from physical disabilities to long-term cognitive, behavioral and social defects. Recently clinical evidence has demonstrated that TBI may frequently cause hypothalamic-pituitary dysfunction. Schneider et al. (2007) reported that the incidence is 31 cases of hypopituitarism per 100 000 cases of TBI and subarachnoid hemorrhage per year.

Changes in pituitary hormone secretion may be observed during the acute post-TBI phase, representing part of the acute adaptive response to the injury. Post-traumatic hypopituitarism is observed in about 40% of patients with a history of TBI (Bondanelli et al., 2005). In most cases there occurs an isolated deficiency of pituitary hormone (mainly gonadotropin and somatotropin).

The most common cause of hypopituitarism is a pituitary tumor (also known as a pituitary adenoma). Pituitary adenomas are almost invariably benign (not cancerous). However, the pituitary adenoma itself may put pressure on the remaining normal part of the pituitary gland and limit or even destroy its ability to produce hormones appropriately. Pituitary adenomas may exert mechanical compression of the portal vessels and the pituitary stalk and cause ischemic and necrotic damage of the anterior lobe of the pituitary. This mechanism is responsible for the occurrence of hypopituitarism.

Pituitary adenomas are classified according to the type of hormone secreted. The classification of pituitary adenomas is shown in Table 5.

Type of adenoma	Secretion	Pathology
Corticotrophic adenomas	ACTH	Cushing's disease
Somatotropic adenomas	GH	Acromegaly
Thyrotrophic adenomas (rare)	TSH	Hyperthyroidism usually doesn't cause symptoms
Gonadotropic adenomas	LH, FSH and their subunits	Usually doesn't cause symptoms
Prolactinomas	PRL	Amenorrhea, infertility galactorrhea
Null cell adenomas (Incidentalomas)	Do not secrete hormones	No symptoms

Table 5. Classification of pituitary tumors based on hormone levels

Hypopituitarism can also result from pituitary surgery, which might damage part of the normal pituitary. It can also result from radiation treatment. The pathway by which radiation induces hypopituitarism is largely unresolved. Attempts to explain the mechanism causing the damage take into account the direct neuronal damage, and altered neurotransmitter input from other brain centers. Other tumors that grow near the pituitary gland (e.g., craniopharyngioma, Rathke's cleft cyst) can cause hypopituitarism. In addition, tumors that metastasize from cancers elsewhere in the body can spread to the pituitary gland and can lead to hypopituitarism.

Inflammation of the pituitary can also cause hypopituitarism. Sarcoidosis and histiocytosis are types of chronic inflammation that also can result in hypopituitarism (Table 4).

Congenital hypopituitarism can range from mild, involving deficiency of a single hormone, through more severe phenotypes affecting multiple pituitary hormone axes, to panhypopituitarism.

Isolated growth hormone deficiency is the most common manifestation, affecting between 1 in 4000 and 10 000 live births. Normal anterior pituitary development is dependent upon a complex genetic cascade of signaling molecules and transcription factors. Mutations in several of these genes are associated with congenital hypopituitarism. In several cases, different mutations within the same gene have been reported to lead to variable phenotypes. Kelberman and Dattani (2006) presented details of the mutation and their consequences in their excellent review paper. For example, of interest is the detection of a new mutation of LHX3 presented by Rajab et al. (2008). They describe four patients from two unrelated consanguineous pedigrees with novel mutations in the LIM homeodomain transcription factor LHX3. All four patients presented with early-onset hypopituitarism and neonatal hypoglycemia. Subsequent clinical evaluation revealed that all four patients exhibited varying degrees of sensorineural hearing loss.

### 7.1 Diagnosis and clinical presentation

Hormone deficiency is diagnosed based on the patient's symptoms (Table 3). When a pituitary adenoma or other tumor is detected near the pituitary, or when a person is

exposed to some other potential cause of hypopituitarism, the patients should be evaluated for hypopituitarism. Tumors in the sellar region with suprasellar extension can manifest with visual impairment. Headaches are another symptom of tumor masses. Infrequent symptoms of tumor expansion are oculomotor nerve impairment and damage to other cranial nerves. Brain damage can cause neurological deficits, weight changes, depression, sleep disturbances, and loss of drive (Schneider et al., 2007). Symptomatic patients should undergo blood and sometimes urine tests. The most important tests helping to determine specific pituitary hormone deficiencies are summarized in Table 6. Cranial and pituitary

<b>Corticotropic function</b>	
Morning cortisol	< 100 nmol/l: hypocortisolism > 500 nmol/l: hypocortisolism excluded
Morning ACTH	Below upper reference range secondary adrenal insufficiency
250 µg ACTH test	Cortisol < 500 nmol/l after 30 min
<b>Thyrotropic function</b>	
Free thyroxine	Low (<11 pmol/l)
TSH	Low or normal (occasionally slightly raised)
<b>Gonadotropic function</b>	
Estradiol	Low (< 100 pmol/l)
LH and FSH	Low (< 2 mIU/ml)
Postmenopausal	FSH inappropriate low
<b>Somatotropic function</b>	
IGF-1	Below or in the normal reference range
Insulin tolerance test	Adults: growth hormone < 3 µg/l Children: growth hormone <10 µg/l Transition phase: growth hormone < 5 µg/l
GHRH+arginine test	Underweight or normal weight (BMI<25): 11.5 µg/l Overweight (BMI >25 to <30): 8.0 µg/l Obese (BMI >30): 4.2 µg/l
GHRH+GHRP-6 test	Growth hormone <10 µg/l
<b>Posterior pituitary function</b>	
Basal urine and plasma sample	Urine volume (>40 ml/kg body weight per day) + urine osmolality <300 mOsm/kg water+ hypernatremia
Water deprivation test	Urine osmolality <700 mOsm/kg; Ratio of urine to plasma <2

Table 6. Criteria for pituitary hormone deficiency (modified by Schneider et al. 2007)

gland magnetic resonance imaging (MRI) should be performed to exclude tumors and other lesions of sellar and parasellar region. Diffusion-weighted MRI and perfusion MRI are advanced techniques that provide information not available from conventional MRI. In particular, these techniques have a number of applications with regard to characterization of tumors and assessment of tumor response to therapy (Provenzale, 2006). Contrast-enhanced images may be needed for the diagnosis of pituitary microadenomas (10 mm).

## 7.2 Treatment

If the hypopituitarism is caused by a lesion or tumors, removal of the tumor or radiation or both are treatment options. Patients who have a large pituitary tumor will occasionally develop a potentially life-threatening condition called pituitary apoplexy. Symptoms typically associated with pituitary apoplexy include sudden severe headache, decreased visual acuity, and ophthalmoplegia. Surgical decompression is an emergency procedure because permanent blindness may result if left untreated.

Transsphenoidal adenectomy surgery can often remove the tumor without affecting other parts of the brain. Endoscopic surgery has become common recently. External radiation is used to kill cancer cells and to shrink tumors. Stereotactic radiation therapy is a new procedure sending focused radiation directly into cancerous tissue. This is a precise technique that targets the cancer tumor, causing less damage to the surrounding tissues. Prolactinomas are most often treated with a dopamine agonist, as will be discussed in the next section of this chapter. Somatotrophic adenomas respond to octreotide, a long-acting somatostatin analog, in many but not all cases. Unlike prolactinomas, thyrotrophic adenomas characteristically respond poorly to dopamine agonist treatment.

Hormone replacement therapy may be required after such a procedure.

Glucocorticoids are required if the ACTH-adrenal axis is impaired. This is particularly important in sudden collapse due to pituitary apoplexy or acute obstetric hemorrhage with pituitary insufficiency. In such circumstances, initiation of a possibly life-saving treatment pending a definitive diagnosis should not be delayed. The emergency measures apply hydrocortisone at a dose of 100-150 mg/day. In chronic treatment hydrocortisone 10-25 mg per day or 25-37.5 mg per day (usually 2-3 doses per day) is used.

Secondary hypothyroidism should be treated with thyroid hormone replacement. The dose of thyroxine should be adjusted so that the free thyroxine level is in the middle-upper normal range and tri-iodothyronine is normal.

In cases of gonadotropin deficiency, replacement therapy with estrogens and progestagens is used. The application of these hormones, as well as ways to induce ovulation with exogenous gonadotropin, are presented in section 3.4. (Hypogonadotropic hypogonadism/management).

Growth hormone deficiency is treated with this hormone after dose adjustment to normal IGF-1 concentrations in the blood. Usually the dose for adults is 0.2-1 mg/day, and the dose for children is 25-50 µg/kg per day.

Diabetes insipidus is treated with desmopressin (0.3-1.2 mg/day oral, and 10-40 µg/day intranasal).

In most cases of hypopituitarism, the disorder is not preventable. Awareness of the risk allows early diagnosis and treatment. Hypopituitarism is usually permanent and requires life-long treatment. Adequate replacement of pituitary hormones can enhance quality of life, and reduces morbidity and mortality associated with this disorder.

## 8. Hyperprolactinemia

Hyperprolactinaemia is one of the most common endocrinological disorders affecting the hypothalamic–pituitary axis. The increase of prolactin level interrupts the pulsatile GnRH secretion and in turn causes disturbances of the menstrual cycle. Hyperprolactinaemia can occur in physiological and pathological conditions.

### 8.1 Prolactin secretion in physiological conditions

Prolactin (PRL) was originally identified as a neuroendocrine hormone of pituitary origin. PRL is a polypeptide hormone that as a result of posttranslational processes may take different forms. The monomeric form is a single chain polypeptide whose molecular weight is 23 kDa. PRL may occur in 50 kDa and 150 kDa molecular variants. These large PRL variants may be secreted predominantly; this condition is termed "macroprolactinemia". It is characterized by high immunological and normal biological serum levels of prolactin, and lack of clinical symptoms of hyperprolactinemia. Macroprolactin is formed by combination of the hormone with immunoglobulin IgG, or its autoantibodies. In normal conditions the monomeric isoform represents 75%-90% of the total hormone. The prolactin gene is located on chromosome 6 and contains 914 base pairs.

Prolactin receptor (PRLR) is a member of the cytokine receptor superfamily. The receptor is present in nearly all organs and tissues. Although the PRLR gene is unique in each species, alternative splicing generates different isoforms. A long PRLR isoform (long-R) and several short PRLR isoforms (short-R) have been detected. PRLR exists as seven recognized isoforms in humans. The role of prolactin in the mammary gland is largely the result of activity of the long-R isoform. It has been proposed that short-R isoforms inhibit the function of long-R, or act as positive regulators in the mammary gland. The mechanisms by which PRL signals through short-R isoforms remains unexplained. The long-R isoform is strongly expressed in the ovary, adrenal gland, kidney, mammary gland, small intestine, choroid plexus and pancreas, but other organs (e.g. liver) also express high levels of the short-R isoform. The various PRLR isoforms exhibit different signaling properties. It is also interesting to note that heterodimerization of different PRLR isoforms produces inactive complexes that might also be physiologically significant because PRL target cells usually express more than a single PRLR isoform.

The role of PRL in human ovarian function is unclear, in large part because no disruptive mutations of human PRL or the human PRLR have been identified. Furthermore, no study has yet compared the distribution of PRLR in human ovaries. Although it is not yet clear how PRL signals in the human ovary, signaling pathways induced by prolactin through its short-R isoform are very likely (Binart et al., 2010).

Hypothalamic regulation of PRL secretion mainly involves tonic inhibition via portal dopamine. This is in agreement with the fact that blockade of dopamine D2 receptors results in increased secretion of the hormone. Evidence suggests that prolactin secretion is regulated by three populations of hypothalamic dopaminergic systems: the tuberoinfundibular, tuberohypophyseal and periventricular hypophyseal dopaminergic neurons.

Prolactin secretion is also mediated by other factors, which stimulate prolactin gene transcription, synthesis of hormone, and its secretion. The most important and best studied of these are estradiol, TRH (thyrotropin releasing hormone), EGF (epidermal growth factor), and VIP (vasoactive intestinal peptide) (Binart et al., 2010). Serotonin (5-HT) has a

stimulatory role in prolactin regulation by mediating suckling-induced rises. The stimulatory effect on prolactin secretion of estrogen is well known. The estrogen receptor binds directly to DNA, which contains an estrogen-responsive element, resulting in rapid stimulation of gene transcription. Estrogens act at the pituitary as well as at the hypothalamic level, affecting the secretion of GnRH by kisspeptin expressing cells. Estrogens can directly modify the neuronal activity of several brain regions which regulate reproduction. It should be emphasized that opioid peptides may mediate some effects of estrogen and thus affect the regulation of PRL secretion.

PRL is secreted in a pulsatile fashion, and it displays a circadian rhythm with nearly three times the increase of the hormone level at night, during sleep. The physiological causes of increased prolactin secretion are summarized in Table 7.

Although the pleiotropic actions of PRL are recognized, its role in regulating growth and differentiation of mammary tissues is better understood. PRL acts synergistically with steroid hormones, stimulates the growth and differentiation of mammary tissues (mammotrophic action), initiates the secretion of milk (lactotropic action), and sustains lactation (lactopoietic action). Experimental studies using animal models allow one to consider the participation of PRL in such physiological activities as behavior and in the brain in general metabolism, immune responses, and electrolyte balance. There are almost 300 functions or targets identified for this hormone in various species, but the question remains open as to which of them are really relevant in humans (Bernichtein et al., 2010). Unfortunately, until now there have not been found disorders related to the genes encoding human PRL or its receptor and therefore we lack a definitive clinical model of isolated PRL deficiency that could be used to completely identify the hormone function. The role of PRL in mammary cancer was suggested several decades ago, mainly based on observations involving animal models. However, a clinical and epidemiological study involving human patients failed to be conclusive. Nevertheless, studies on the role of PRL in breast tumorigenesis are constantly being developed. La Pensee and Ben-Jonathan (2010) in their elegant review presented the suggestion that a reduction in the ability of PRL and estrogens to confer chemoresistance should have several benefits for breast cancer patients, including an increase in the number as well as efficacy of valuable drugs. There is now clear evidence that high-normal circulating PRL levels increase breast cancer risk in both pre-menopausal and post-menopausal women (Bernichtein et al., 2010).

Type of stimulus	Additional explanations
Increased estrogen secretion	Pregnancy, puerperium, lactation, neonatal period
Nipple stimulation	Mechanical and during breast-feeding
Stimulation of the uterine cervix	Sexual intercourse
Sleep	Circadian rhythm
Stress, exercise and hypoglycemia	

Table 7. Physiological causes of increased PRL secretion

## 8.2 Hyperprolactinemia – laboratory results or pathology symptom?

Pathological hyperprolactinemia is defined as circulating PRL levels above the normal range, which occurs in conditions other than pregnancy and lactation, when hyperprolactinemia is due to physiological factors (Table 8).

Before a diagnosis of hyperprolactinemia can be made, it is necessary to exclude laboratory errors related to the technique for hormone assay, but also to the conditions of sampling. It is important that the sample of blood was collected in basal conditions after 11 o'clock in the morning, so as to eliminate early morning growth hormone associated with the circadian rhythm of secretion. In the final evaluation of the results it is important to incorporate three facts:

1. Hormone concentrations in blood (50-100  $\mu\text{g/L}$  = average increase, > 100  $\mu\text{g/L}$  = significant increase).
2. Presence or absence of circadian hormone secretion.
3. At high values, exclusion of macroprolactin.

Regardless of its cause, the degree of PRL increase correlates with the severity of hypogonadism. Serum concentrations of PRL greater than 100  $\mu\text{g/L}$  are associated with amenorrhea. A PRL level of 50-100  $\mu\text{g/L}$  can be associated with either amenorrhea or oligomenorrhea, and a level of 20-50  $\mu\text{g/L}$  can result in shortening of the luteal phase (Helm et al., 2009). Absence of a circadian rhythm indicates tumors or macroprolactin as the cause of hyperprolactinemia. Macroprolactin diagnosis is based on the polyethylene-glycol (PEG) test.

In seeking the cause of pathological hyperprolactinemia, pharmacotherapy causing increased secretion of this hormone should be excluded. A significant increase in PRL is observed with therapeutic doses of neuroleptics, opiates, antidepressants, antihypertensives, antihistamines, and oral contraceptives. Low daily dosing regimens (e.g. 200 mg chlorpromazine), conventional antipsychotics or risperidone can cause significant prolactin elevations. A number of other agents are in development. Clozapine, quetiapine and olanzapine are reported either to cause no increase in prolactin secretion at all or to increase it only transiently and mildly. In contrast, risperidone and amisulpride cause a marked and sustained increase in serum prolactin levels. Conventional antipsychotic agents differ in their ability to pass the blood-brain barrier. Because the pituitary gland lies outside this barrier, one would expect that drugs with poor brain penetrability and higher serum concentrations such as sulpiride would have a greater effect on pituitary prolactin secretion. Antidepressants with serotonergic activity, including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and some tricyclic antidepressants, can cause modest elevations of prolactin levels and have the potential to elevate prolactin levels above the threshold (Wieck & Haddad, 2003). The main drugs that can cause hyperprolactinemia are summarized in Table 8.

The major cause of pathological hyperprolactinemia involves tumors of pituitary lactotroph cells (prolactinomas). Prolactin-secreting pituitary tumors also include GH-producing pituitary tumors, which in 25% of cases co-secrete PRL. Prolactinomas are classified as microadenomas (<10 mm) or macroadenomas (>10 mm).

Macroprolactinomas are frequently characterized by suprasellar penetration, and increased secretion of PRL. High PRL level may mean cavernous sinus invasion, and resistance to dopamine agonist. A serum cutoff level of 3300  $\mu\text{g/L}$  predicts an invasive tumor with specificity of 91% (Helm et al., 2009).

Prolactinoma development is presently being studied employing molecular biological techniques; the question of whether tumorigenesis can be attributed to specific defects of gene regulation remains to be answered.

<i>Neuroleptics</i>	Phenothiazines Thioxanthenes Butyrophenones Atypical antipsychotics
<i>Antidepressants</i>	Tricyclic and tetracyclic antidepressants Monoamine oxidase inhibitors Selective serotonin reuptake inhibitors Other
<i>Opiates and cocaine</i>	
<i>Antihypertensive medications</i>	Verapamil Methyldopa Reserpine
<i>Gastrointestinal medications</i>	Metoclopramide Domperidone Histamine receptor blockers (?)
<i>Protease inhibitors (?)</i>	
<i>Estrogens</i>	

(?) - Case reports only

Table 8. Medication that may cause hyperprolactinemia (Helm et al. 2009)

Hyperprolactinemia also occurs in other types of adenomas, such as multihormonal adenomas, as well as in tumors of the pituitary stalk. Hyperprolactinemia accompanies diseases such as chronic renal failure, liver cirrhosis, epilepsy, polycystic ovary syndrome and chest injuries.

### 8.3 Treatment

The main goal of treatment of hyperprolactinemia is to eliminate symptoms through reduction of prolactin secretion. The largest group of patients needing treatment is that of women with micro- and macroprolactinoma. Treatment should lead to normalization of PRL levels, restoration of ovary function, reduction of tumor size, and recovery of pituitary function. Currently available medications to treat symptomatic hyperprolactinemia, mainly caused by prolactinomas, are dopamine agonists and include bromocriptine, quinagolide, and cabergoline. Pergolide is no longer used because of the finding that patients with Parkinson's disease who were treated with this dopamine agonist had increased risk of valvular heart diseases.

Bromocriptine (BEC) is generally considered to be the agent of choice in the treatment of prolactinomas, because it is well tolerated, and may be used chronically, over a long period of time. BEC is a safe medicine that effectively reduces the synthesis and secretion of PRL. Treatment begins with a low dose (1.25-2.5 mg/day) and then gradually increases to the minimum effective dose. The average daily dose is 2.5-15 mg, although about 30% of patients with macroadenomas require increased doses of 20-30 mg/day. It is usually used in 2-3 divided doses throughout the day. In approximately 80% of patients BEC effectively

decreases the plasma PRL levels, and also reduces tumor size by 50% in 70% of cases. A limitation of the use of BEC is side effects such as dizziness, nausea, and vomiting. It is estimated that about 15% of patients are completely unable to tolerate therapeutic doses of BEC. In contrast to patients with microprolactinoma, in cases of macroprolactinoma the extent of reduction in tumor size is not well correlated with the change in plasma PRL levels which always precedes tumor shrinkage, and patients who do not show a drop in PRL do not have any tumor shrinkage (Babu Segu, 2011).

Another drug used in cases of hyperprolactinemia is the non-ergot dopamine agonist quinagolide, which has a long duration of action. The advantage of the drug is a lower number of adverse events than in the case of BEC with comparable efficacy. Tolerance of the drug may be reduced by alcohol. Treatment begins with a dose of 25 µg/day, which is increased in 3 consecutive days to 75 µg/day. In case of unsatisfactory results of treatment it can be increased to 150 µg/day. It is given as one dose per day.

In patients who do not respond to BEC or who cannot tolerate both the drugs mentioned above, a long-acting dopamine agonist, cabergoline, can be used. It is well tolerated, and its efficacy profiles are somewhat superior to those of BEC and quinagolide. It can be administered twice a week, with the usual starting dose of 0.25 mg biweekly to a maximum dose of 1 mg biweekly. As an adjunct or second line therapy of acromegaly, cabergoline has low efficacy in suppressing growth hormone levels and is highly efficient in suppressing the hyperprolactinemia that is present in 20-30% of acromegaly cases. It has at times been used as an adjunct to SSRI antidepressants as there is some evidence that it counteracts certain side effects of those drugs, such as reduced libido and anorgasmia. It has also been suggested that it has a possible use to control gynecomastia caused by elevated prolactin levels, through the use of anabolic steroids. Additionally, a systematic review and meta-analysis concluded that prophylactic treatment with cabergoline reduces the incidence, but not the severity, of ovarian hyperstimulation syndrome (Youssef et al., 2010).

Side effects are mostly dose dependent. Much more severe side effects are reported for treatment of Parkinson's disease with cabergoline, but when it is used for treatment of hyperprolactinemia and other endocrine disorders or gynecologic indications where the typical dose is significantly lower, the side effects are smaller. The list of possible, though rare side effects of treatment with cabergoline include nausea, constipation, dry mouth, vomiting, dyspepsia, insomnia, depression and very rarely dyskinesia and hallucinations. In two studies published in the *New England Journal of Medicine* on January 4, 2007, cabergoline was implicated along with pergolide in causing valvular heart disease (Schade et al., 2007; Zanettini et al., 2007). Both drugs are ergot-derived dopamine agonists, although their molecular skeletons are different. As a result of this, cabergoline is not approved in the U.S. for Parkinson's disease, but for hyperprolactinemia the drug remains on the market. The lower doses required for treatment of hyperprolactinemia have been found not to be associated with clinically significant valvular heart disease or cardiac valve regurgitation (Food and Drug Administration Public Health Advisory, 2007).

Transsphenoidal pituitary adenectomy is the preferred surgical treatment in patients with microprolactinoma and in most patients with macroprolactinoma. A transcranial approach is used in patients with large extrapituitary extension. Indications for neurosurgical treatment of prolactinoma are limited to specific clinical situations. These situations are: microadenoma in women desiring pregnancy and who cannot tolerate BEC, lack of consent of a patient with chronic long-term medication with BEC or other dopamine agonist, and lack of response to pharmacological treatment used, or occurrence of progression after an initial response.

Indications for emergency neurosurgical treatment are the states which were described in the section on hypopituitarism in this chapter. After surgical treatment the recurrence rate is about 15%-20%. Mortality and morbidity rates are less than 1% and 6%, respectively (Babu Segu , 2011). Pharmacological therapy of prolactinoma should be monitored for serial assay of plasma PRL levels, which should be repeated at least every two months. MRI, especially in cases of treated macroprolactinoma, should be repeated at least once a year.

## 9. Androgen excess in women

Androgen excess is one of the most common endocrine disorders of young women. According to the literature, these conditions apply to 7-10% of reproductive-aged women (Frank, 1995 ; Azziz et al., 2004 a; Abdel-Rahman & Hurd, 2010). Patients with androgen excess represent approximately 18% of hospitalizations in the department of gynecological endocrinology. The main reasons for the patients to undergo medical examinations are as follows: oligo/amenorrhea, ovulatory dysfunction, excess body and facial terminal hair growth, acne, alopecia, obesity and infertility. Many specific underlying disorders can be identified in androgen excess women. The above-mentioned causes are summarized in Table 9.

Polycystic ovary syndrome Hyperandrogenism, insulin resistance, and acanthosis nigrans (HAIR-AN) syndrome Ovarian hyperthecosis Androgen secreting ovarian tumors
Congenital adrenal hyperplasia (CAH) and nonclassic adrenal hyperplasia (NCAH) Cushing syndrome Androgen secreting adrenal tumors
Functional androgen excess Idiopathic hirsutism Hyperprolactinemia Pregnancy Exogenous androgens

Table 9. Cause of androgen excess in women

### 9.1 Androgens: definitions and sources of their synthesis

Chemical compounds called androgens stimulate growth of male genitals. According to another definition, androgens are hormones supporting male sexual behavior in castrated animals. These hormones can be defined as androgen receptor ligands that can regulate gene expression, thus affecting their own performance. The androgen receptor was discovered in 1970, and the gene that encodes it was cloned in 1988. The androgen receptor gene is located on the long arm of chromosome X. There are two isoforms of the androgen receptor (AR-A and AR-B). Both isoforms are present in almost all tissues and organs of the body. The highest affinity with the receptor is shown by dihydrotestosterone (DHT), lower by testosterone, and still lower by dehydroepiandrosterone and androstenedione. The adrenal glands and ovaries secrete five androgens through a similar pathway: testosterone, dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, and androstenediol, the latter of which has both androgenic and

estrogenic activity ( Labrie, 2010). Testosterone and its biologically active metabolite dihydrotestosterone (DHT) are the only active androgens. DHEAS, DHEA, and androstenedione are all precursors of testosterone.

The ovaries produce 25% of circulating testosterone, whose secretion is controlled by LH. The ovaries also secrete 50% of the androstenedione and 20% of DHEA. The adrenal glands produce all the DHEAS, 80% of the DHEA, 50% of androstenedione and 25% of circulating testosterone, mainly via conversion of androstenedione to testosterone. DHEAS and 11-androstenedione are not secreted by the ovaries and therefore are used as markers of adrenal androgen secretion. Adrenal androgen secretion is controlled by ACTH. PRL and estrogen can affect adrenal androgen production (Abdel-Rahman & Hurd, 2010). Clinical manifestation of androgen excess may be the result of growth of androgen production, increase of receptor sensibility (receptor expression), and increased activity of 5- $\alpha$ -reductase (the enzyme responsible for converting testosterone to dihydrotestosterone).

## 9.2 Clinical features of androgen excess patients

The main symptoms of androgen excess in women are summarized in Table 10. Azziz et al. (2004 a) published a clinical study of over 1000 patients with symptoms of androgen excess. Complete relevant information could be obtained from the authors of 873 patients and they were included in the study. Oligo-ovulation was present in 88.2% of patients, most of whom showed menstrual disorders, mainly oligomenorrhea.

Defeminization symptoms	Oligo/amenorrhea, anovulation, infertility
Masculinization symptom	Hirsutism, acne, androgenic alopecia, clitoromegaly, increased muscle mass, lower tone of voice, masculine habitus
Metabolic disorders	Obesity, glucose intolerance, insulin resistance, lipid disorders, acanthosis nigricans

Table 10. Main symptoms of androgen excess in women

Most published studies support the view that the presence of hirsutism is a strong indicator of androgen excess (Azziz et al., 2006; Yidiz et al., 2010). Hirsutism refers to the occurrence in women of terminal hairs in characteristically masculine areas. Terminal hairs demonstrate regional morphological differences. Their growth and development is primarily stimulated by GH and thyroid hormones, and depending on body region, also by androgens (Yidiz et al., 2010). The optimal androgen effect requires the presence of normal androgen receptor and 5 $\alpha$ -reductase function, although testosterone in sufficient concentration can also exert a direct effect on the hair follicle without the involvement of 5- $\alpha$ -dihydrotestosterone. 5- $\alpha$ -reductase, as both of its isoenzymes (type I and type II), is present in dermal papillae of the lower abdomen in hirsute women, and its activity was demonstrated to be regulated by androgens (Skalba et al., 2006).

The identification and assessment of the severity of hirsutism is determined visually using quantification of normal and abnormal hair growth in women. Ferriman and Gallwey (1961) evaluated eleven body areas in normal white women; each body area was scored on a scale

of 0-4. The authors observed that a score of  $>7$ , when summing the scores of all the body areas assessed with the exception of lower arms and legs, was observed in only 4.3% of their population. The results of most clinical studies suggest that 5-7% of unselected women of reproductive age have a point value according to the Ferriman Gallwey score  $>8$ , which can be used as the cut-off value to define hirsutism. It should be noted that hair is second only to skin color as a feature of racial difference. The number of hair follicles per unit skin area and the rate of hair growth vary among ethnic and racial groups. For example, in the population of Asian women (which includes Chinese, Japanese, Koreans, American Indians, and Eskimos) the overall density of facial and body terminal hair growth is lower, and the definition of hirsutism may therefore require a lower cut-off value (Yidiz et al., 2010). However, population studies involving 633 unselected women confirmed that the degree of facial and body terminal hair was similar in black and white women (De Ugarte et al., 2006). A modified Ferriman and Gallwey score, which evaluates nine body areas, is widely used by clinical endocrinologists, because it is a simple and practical method (Hatch et al., 1981). However, moderate to severe unwanted hair growth confined to one or two areas of the body, particularly the upper lip, chin, and lower abdomen, may be a sign of androgen excess (Fig. 2).



Fig. 2. Hirsutism in 37-year-old woman with diagnosed PCOS (A,B,C). Facial hirsutism in 25-year-old woman diagnosed with HAIR-AN syndrome (D).

According to studies cited above, 75.5% of patients with androgen excess had hirsutism, and 14.2% had acne, whereas 29.7% complained of infertility. Patients with infertility were more obese than their non-infertile counterparts (Azziz et al. 2004 a). Various studies have evaluated the impact of obesity on androgen excess in women. It was found that obese hyperandrogenic women are characterized by a significantly lower sex hormone binding globulin (SHBG) plasma level and more severe hyperandrogenemia, in comparison to their normal-weight counterparts. There is, therefore, consistent evidence that increasing body weight may favor a more severe form of disorders of hyperandrogenic women. Epidemiological studies show that the prevalence of obesity in women with androgen excess is within 40%-60% (Pasquali et al., 2007). These women have a tendency to visceral deposition of fat, mainly in the abdomen. Obesity in hypoandrogenic women is associated with metabolic changes, principally insulin resistance and metabolic syndrome. Metabolic syndrome is an integral part of androgen excess in women. In the typical form, it includes insulin resistance, obesity, and altered lipid profile. The molecular mechanism of insulin resistance in this disorder differs from those in other common insulin-resistance states, such as simple obesity, and type 2 diabetes mellitus. In these cases, hyperinsulinemia and subnormal insulin-mediated glucose uptake were observed. Insulin resistance in women with androgen excess is not observed in all tissues. Specifically, it is present in skeletal and adipose tissue, whereas insulin resistance is absent in the ovaries, adrenal glands, liver and skin. The cause of insulin resistance in polycystic ovary syndrome (PCOS) is considered to be a defect of the insulin receptor and insulin signaling in the post-receptor pathways. The defect lies in reduced autophosphorylation of the insulin receptor, secondary to excessive phosphorylation of serine residues of this receptor, which impairs its function and reduces further transmission of the signal. In addition, compensatory hyperinsulinemia exerts an androgen stimulatory effect on the ovaries and adrenal glands. Insulin resistance occurs more in obese hyperandrogenic women, but it can also occur in lean hyperandrogenic women. Dunaif et al. (1989) demonstrated that obese and lean hyperandrogenic women were both more insulin resistant than BMI-matched normal controls.

## **10. Polycystic ovary syndrome (PCOS)**

### **10.1 PCOS – definition and epidemiology**

PCOS is a very common endocrinopathy with heterogeneous presentation, whose etiology is unclear. The formulation of a precise definition is therefore difficult, and diagnostic criteria for PCOS remain controversial. After reviewing the literature, the most convincing seems to be the definition proposed by Azziz (Azziz, 2007): “Polycystic ovary syndrome (PCOS) is a heterogeneous disorder, whose principal features include androgen excess, ovulatory dysfunction, and/or polycystic ovaries”.

Establishing the diagnosis of PCOS requires the exclusion of other androgen excess and ovulatory disorders of clearly defined etiologies. The list of disorders that require exclusion are nonclassic adrenal hyperplasia, which will be discussed later in this chapter, adrenal or ovarian androgen-secreting tumors, Cushing's disease and use or abuse of androgenic or anabolic drugs. The functional disorder resulting in clinical features suggestive of androgen excess, namely idiopathic hirsutism, should also be excluded. Causes of hyperandrogenism in women are shown in Table 9.

Ovulatory dysfunction is generally detectable by the presence of clinically evident oligo-amenorrhea, although about 20-30% of eumenorrhea PCOS women will present oligo-anovulation.

Ultrasound diagnosis of polycystic ovaries is often inconsistent with accepted criteria, and thus inappropriate. In addition, an ultrasound symptom of polycystic ovaries also occurs in other clinical situations.

It should be emphasized that PCOS is, by its nature, a set of symptoms, signs and biochemical features that can occur in various combinations. Deciding what combination of pathological features is sufficient for the diagnosis of PCOS was the subject of consultation of experts. The first definition of PCOS was determined by an expert conference sponsored by the US National Institutes of Health (NIH) in 1990 (Azziz, 2007). In May 2003 a group of experts in the field of PCOS, which gathered in Rotterdam for a conference sponsored jointly by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, established the first agreed definition of PCOS (the Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004). The resulting statement of this conference constituted criteria, known as the "Rotterdam criteria", which are now commonly used in practice and the literature for defining PCOS. Some experts believe, however, that the Rotterdam Criteria do not resolve all controversies concerning the definition of PCOS (Franks, 2006). The discussion is whether hyperandrogenic women with polycystic ovaries and regular cycles should be included in the definition established in Rotterdam. Another, in my opinion, very important issue is to determine whether PCOS women with chronic anovulation without evidence of androgen excess should be defined as part of the syndrome. Opinions on this matter are varied. Certainly, the combination of hyperandrogenism and chronic anovulation provides a widely accepted basis for the diagnosis of PCOS. It was observed that PCOS women with hyperandrogenism and regular cycles are less likely to have insulin resistance and hyperinsulinemia than those with chronic anovulation (Franks, 2006). Obese women with PCOS are more likely to be anovulatory than lean hyperandrogenic subjects. These observations indicate the relationship between metabolic disorders and the maturation of ovarian follicles. With regard to the controversy over the definition of PCOS, the Androgen Excess Society (AES) recommend an evidence-based definition for this disorder. According to all available data, PCOS should be diagnosed according to the presence of three features: (a) androgen excess (clinical and/or biochemical hyperandrogenism), (b) ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology), and (c) exclusion of other androgen excess or ovulatory disorders (Azziz et al., 2006). PCOS diagnostic criteria established by the three expert groups are summarized in Table 11.

According to the Rotterdam criteria there are four different phenotypes of PCOS patients, whereas in the AES criteria the phenotype of patients with PCOS is the only one (Figure 2).

New proposed additions to and at the same time simplifications of the diagnostic criteria for PCOS are the inclusion of plasma AMH levels, and calculation of the follicle number (Dewailly et al., 2010).

The prevalence of PCOS will depend to a degree on the criteria used to define this disorder. Using the NIH criteria in unselected women of reproductive age, the prevalence of clinically evident PCOS ranges from 6.5 to 8%. The racial difference was not statistically different (Azziz, 2007), although recently it has been suggested that PCOS is more prevalent in women of South Asian descent, based on clinical findings in South Asian immigrants and women in Britain (Chang 2009 a). The prevalence of PCOS according to the Rotterdam and AES criteria appears to be over 60% larger than the group classified as PCOS by the NIH definition. Approximately 80-90% of women with excess androgen have PCOS (Azziz et al., 2004 b; Denny et al., 2010). There are many factors influencing the prevalence of PCOS, such as metabolic disorders, premature adrenarche, and gestational diabetes.

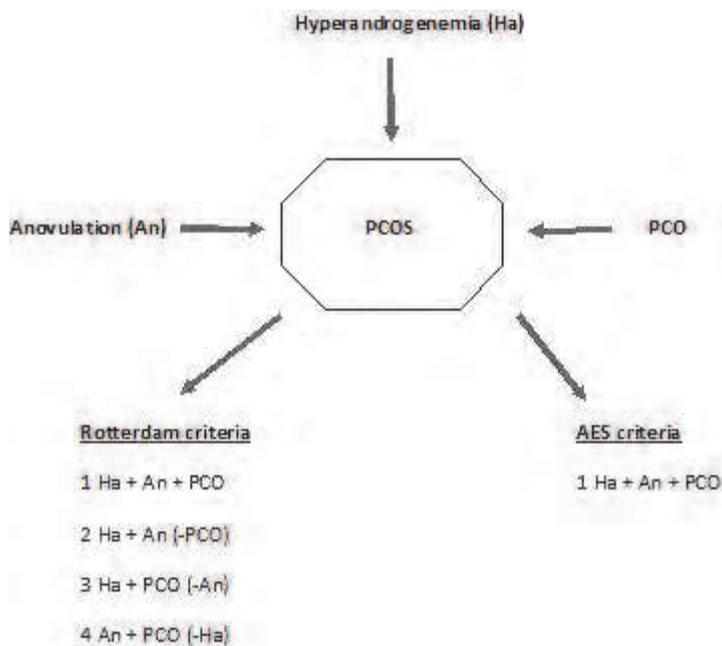


Fig. 3. PCOS phenotypes according to Rotterdam and AES criteria.

<p>NIH 1990</p>	<p><b>To include all of the following:</b></p> <ul style="list-style-type: none"> <li>• Clinical hyperandrogenism and/or hyperandrogenemia</li> <li>• Chronic anovulation</li> </ul> <p>Exclusion of related disorders</p>
<p>ESHRE/ASRM (Rotterdam) 2003</p>	<p><b>To include two of the following, in addition to exclusion of related disorders:</b></p> <ul style="list-style-type: none"> <li>• Oligo-anovulation</li> <li>• Hyperandrogenism and/or hyperandrogenemia</li> </ul> <p>Exclusion of related disorders</p>
<p>AES 2006</p>	<p><b>To include all of the following:</b></p> <ul style="list-style-type: none"> <li>• Hyperandrogenism (hirsutism and/or hyperandrogenemia)</li> <li>• Ovarian dysfunction (oligo-anovulation and/or polycystic ovaries)</li> <li>• Exclusion of related disorders</li> </ul>

NIH - US National Institutes of Health, ESHRE - European Society for Human Reproduction and Embryology, ASRM - American Society of Reproductive Medicine, and AES - Androgen Excess Society.

Table 11. Criteria for defining PCOS by Azziz (2007)

## 10.2 PCOS etiology

PCOS appears to have a complex, multifactorial etiology, wherein multiple predisposing genes interact with environmental and lifestyle factors responsible for the occurrence of disease symptoms constituting part of PCOS. Family studies demonstrate that PCOS is significantly more prevalent among family members than in the general population (Goodarzi, 2007). In both female and male first-degree relatives of patients with PCOS there occur more frequently than in the general population hormonal disorders, metabolic and phenotypic characteristics, such as premature balding in men and symptoms of hyperandrogenism in women. Hyperandrogenemia has been reported in 46% of sisters of PCOS women, of whom 22% were diagnosed with full-blown PCOS. Also in mothers of women with PCOS hyperandrogenemia was found. Moreover, in families of women with PCOS metabolic abnormalities are observed such as obesity, insulin resistance, and abnormal carbohydrate and lipid metabolism.

Numerous publications have allowed the compilation of a list of candidate genes responsible for different phenotypes of PCOS. The basis for creating a list of candidate genes is a hypothetical role of individual genes in PCOS, and the probability that polymorphisms are associated with the phenotype in populations or in families. These gene lists of candidates, constantly updated, can be found in numerous publications (Goodarzi, 2007 ; Wang et al., 2009; Panneerselvam, 2010). As a result, despite a large number of positive reports, no particular gene is universally recognized as significantly contributing to PCOS risk. The problem with PCOS is that the causes of it are still fundamentally unknown.

## 10.3 Clinical evaluation of PCOS

It has been estimated that approximately 75% of patients with PCOS have menstrual dysfunction, but approximately 20% of women diagnosed with PCOS will present with a history of apparent eumenorrhea. In most PCOS women with eumenorrhea anovulation occurs, but it may be prudent to confirm this in a repeated study.

Elevated circulating androgen levels are observed in approximately 60-80% of PCOS patients. The measurement of circulating androgen levels, including free testosterone and free androgen index (FAI), has been used only as an adjuvant for the diagnosis of hyperandrogenic disorders and never as the sole criterion for diagnosis. In fact, 20-40% of women with PCOS will have androgen levels within the normal range.

Clinical features of hyperandrogenism frequently seen in PCOS include hirsutism, acne, and androgenic alopecia. The diagnosis and assessment of severity of hirsutism are discussed above. Acne affects 15-25% of PCOS patients, although it is unclear whether the prevalence of acne is significantly increased in these patients compared to the normal population of similar age. Androgenetic alopecia is rare in patients with PCOS; possibly the incidence of this symptom is about 5% (Azziz et al., 2006).

Current data suggest that polycystic ovaries detected by ultrasound examination may be found in approximately 75% of PCOS women. This high percentage may be associated with false-positive test results. Ultrasound diagnosis of PCOS requires strict criteria. The criteria to define PCOS should include at least one of the following: either 12 or more follicles measuring 2-9 mm in diameter, or increased ovarian volume ( $>10\text{ cm}^3$ ).

If there is a follicle  $>10\text{ mm}$  in diameter, the scan should be repeated at a time of ovarian quiescence in order to calculate the volume and area (Fig. 4).

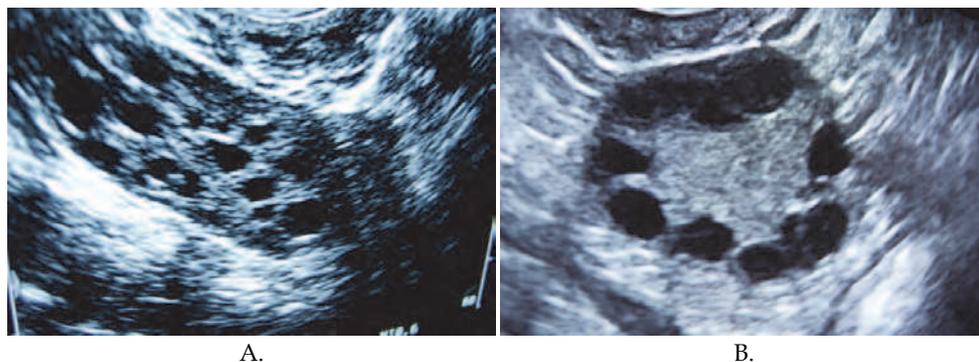


Fig. 4. Sonography scans of polycystic ovaries (PCO)- A. central distribution of follicles, B. peripheral distribution of follicles.

The presence of a single polycystic ovary (PCO) is sufficient to establish the diagnosis. The distribution of follicles and a description of the stroma are not required in the diagnosis (Balen et al., 2003). However, note that PCO is a common, age-dependent finding among ovulatory women. The prevalence of PCO by AFC (antral follicle count) was 32% and decreased with age (Johnstone et al., 2010). Starting from the first descriptions of morphological changes in the ovary, we know that they are enlarged, with numerous peripheral small antral follicles and increased central stroma. It has been proposed that normal follicular growth appears to occur up to the mid-antral stage, after which maturation ceases. Stopping follicular maturation, however, does not prevent apoptosis, although it is not known if it will delay it. Several studies confirm that the plasma level of AMH in PCOS women is 2-3 times higher than in healthy women of similar age. We also know that this level correlates with the number of small antral follicles and plasma androgen levels. I have also observed that the characteristic reduction in AMH levels with age is delayed in PCOS women compared to their healthy peers (unpublished investigation). The evidence presented indicates the involvement of androgens in follicular development.

Obesity, insulin resistance and hyperinsulinism, the symptoms already discussed above, occur in a large proportion of PCOS patients. The PCOS-related insulin resistance state is associated both with decreased ability of insulin to stimulate glucose delivery to target cells and with reduction of glucose response to a given amount of insulin. In fact, a reduction of the transporter GLUT-4 expression in the insulin target tissues has been demonstrated (Palomba et al., 2009).

Abnormalities of lipid metabolism in PCOS include reduced levels of HDL cholesterol and increased LDL cholesterol and triglycerides. It seems that dyslipidemia develops secondary to insulin resistance, because insulin affects the regulation of lipoprotein lipase activity and lipid pathways of change.

#### 10.4 PCOS laboratory and sonographic evaluation

Azziz (2007) proposes to divide the patients suspected of having PCOS into three subgroups, and for each of them to apply the appropriate diagnosis as follows.

- a. Women with overt long-term oligomenorrhea and hirsutism: these women basically have PCOS, pending exclusion of related disorders. Circulating TSH, PRL, and 17OHP

- (17-hydroxyprogesterone) levels should be determined. If these values are normal, then the patient is presumed to have PCOS. Androgen levels and ovarian ultrasonography, while of some value, are not critical to establish the diagnosis.
- b. Women with overt long-term oligomenorrhea, but no obvious sign of androgen excess. Circulating androgen levels (total and free testosterone, and DHEAS) should be determined, and if elevated, assessment of TSH, PRL, and 17OHP should be made. If these latter values are normal, then the patient is presumed to have PCOS. In these women the use of ovarian ultrasonography will not alter the diagnosis.
  - c. Women with hirsutism but apparent eumenorrhea: these women should undergo confirmation of ovulation (determination of progesterone in the luteal phase). They should also undergo ovarian ultrasonography. If the patient is found to have anovulation or polycystic ovaries, they should have TSH, PRL and 17OHP assessed. If these values are normal, then the patient is presumed to have PCOS (classic if anovulatory, or ovulatory PCOS if she has polycystic ovaries but normal ovulation).

It seems obvious that PCOS cannot be diagnosed by symptoms alone. As is apparent from the above proposals of Azziz, depending on the symptoms, appropriate tests should be used. Most often, the following hormone levels are measured when considering a PCOS diagnosis: LH, FSH, PRL, total and free testosterone, FAI (free androgen index), DHEAS, androstenedione, progesterone, estradiol, TSH and 17OHP.

Correct values for levels of **LH**, **FSH**, estradiol and progesterone are presented in Section 2.3 (Menstrual cycle). In some PCOS women the LH level is about 18 IU/L and FSH is about 6 IU/L. This situation is called an elevated LH to FSH ratio or 3:1 ratio. This result is sufficient for ovulation inhibition. Currently, changes in pituitary gonadotropin plasma levels are not included in the diagnostic criteria, although they are still an important test for the evaluation of complex disorders associated with PCOS. LH excess worsens hyperandrogenism through ovarian stimulation of androgenesis. LH excess has long been considered the cause of increased ovarian androgen secretion, but presently its primary role is arguable. There is in fact evidence that ovarian theca cells are capable of androgen production regardless of the stimulation of LH. All observations suggest that dysregulation of androgen biosynthesis is an intrinsic property of PCOS theca cells, and excess LH may be a consequence of the metabolic alterations in PCOS (Doi, 2008).

There are two methods to measure testosterone levels: **total testosterone**, and **free testosterone**. Total testosterone refers to the amount of all testosterone, including free testosterone. The range for this is 6.0-86 ng/dl (according to some methods up to 100 ng/dl). Free testosterone refers to the amount of testosterone that is unbound and actually active in the body. This is usually in the range 0.7-3.6 pg/ml. PCOS women often have increased levels of both total and free testosterone (usually slightly, although sometimes up to the level of older men).

Information on the current circulating free androgens can be obtained by calculating the **free androgen index (FAI)**. FAI is the quotient of the plasma concentration of total testosterone to plasma concentration of sex hormone binding globulin (SHBG), multiplied by 100%. Normal values should not exceed 5%.

**SHBG is a glycoprotein** that binds reversibly and with high affinity to the main biologically active circulating androgen testosterone, and somewhat less well with active estradiol. Its plasma concentrations being regulated by, among other things, androgen/estrogen balance, thyroid hormones, insulin and dietary factors, it is involved in transport of sex steroids in plasma, and its concentration is a major factor regulating their distribution between the

protein-bound and free states. It was originally described as a hepatically secreted protein, and it also functions as part of a novel steroid signaling system that is independent of the classical intracellular steroid receptors. Unlike the intracellular steroid receptors that are ligand-activated transcription factors, SHBG mediates androgen and estrogen signaling at the cell membrane by way of cAMP (Kahn, 2003).

SHBG may be important both physiologically and in a number of endocrine disorders including PCOS (Anderson, 1974). A little of the testosterone is bound to corticosteroid-binding globulins (CBG); however, the main fraction of testosterone in plasma is bound to SHBG. In female plasma the SHBG concentration is twofold higher and the testosterone concentration tenfold lower than in men. SHBG is a glycoprotein, and its molecular weight has been variously estimated at 95 000. It was proved that estrogens stimulate and androgens inhibit SHBG production in the liver. It appears that the balanced increase in estrogen and androgen production in PCOS women causes only a small fall in SHBG. In hirsute women regardless of their menstrual history, a reduction in plasma levels of SHBG takes place. In these women, SHBG concentration may be reduced in over 80%. This finding is independent of the presence or absence of polycystic ovaries (PCO). Low SHBG levels in PCOS are intimately associated with BMI, suggesting that some signals from the adipose tissue, independent of adiponectin and leptin, may regulate liver production of SHBG. In many cases low SHBG levels are associated with a rise in plasma testosterone and other  $17\beta$  hydroxy-androgens. Measurement of SHBG is useful in the evaluation of mild disorders of androgen metabolism and enables identification of those women with hirsutism who are more likely to respond to estrogen therapy.

Evidence suggests that hyperinsulinemic insulin resistance may increase serum levels of ovarian androgens and reduce sex hormone-binding globulin (SHBG) levels in women. Reasoned opinions are, therefore, that a low SHBG level is a strong risk marker for dysglycemia in women, independently of both adiponectinemia and insulinemia (Bonnet et al., 2009). SHBG may therefore improve the identification of women at risk of diabetes. Metabolic syndrome in women is associated with lower SHBG levels (Brand et al., 2011). SHBG levels are low in myxedema, acromegaly, Cushing syndrome, hyperprolactinemia and in obese women.

SHBG levels rise markedly in pregnancy to some 5-10 times those in normal non-pregnant women. SHBG plasma levels are also higher in cases of cirrhosis and thyrotoxicosis (Anderson, 1974).

Thyroid hormones produce an elevation of SHBG in normal subjects and in hirsute women.

**Dehydroepiandrosterone sulfate (DHEAS)** is an androgen that is secreted by the adrenal glands. Normal hormone levels in women show a wide range between 35 and 430  $\mu\text{g}/\text{dl}$ . DHEAS secretion decreases from the age of 30 years and is already decreased, on average, by 60% at the time of menopause. In addition, there is a large variability in the circulating levels of DHEAS and therefore recognition of the hormone deficit is difficult (Labrie, 2010).

Most PCOS women tend to have DHEAS levels greater than 200  $\mu\text{g}/\text{dl}$  (Sterling, 2011). Values above 800  $\mu\text{g}/\text{dl}$  show the need for more accurate diagnosis, because it may indicate an adrenal tumor. Elevated plasma DHEAS levels in PCOS women were associated with the presence of acne and a significantly reduced risk of abdominal obesity, independent of serum testosterone concentration and insulin resistance (Chen et al., 2011).

**Androstenedione** is a hormone that is produced by the ovaries and adrenal glands. Normal plasma levels of androstenedione in women of reproductive age in the early follicular phase

of the menstrual cycle range between 0.9 and 3.4  $\mu\text{g/l}$ . It is believed that determination of the hormone in the blood, as well as the assessment of the ratio of androstenedione to dehydroepiandrosterone, is more important for the differentiation of PCOS and nonclassic adrenal hyperplasia (NCAH) than to diagnose this first.

**17-hydroxyprogesterone (17-HP)** determination in the blood of patients with androgen excess is used as a screen for NCAH. The blood samples should be obtained in the morning, and, most importantly, in the follicular phase of the menstrual cycle. Before the 17-HP assay corticosteroids medication should be discontinued. If the screening 17-HP level is  $>1.7 \mu\text{g/l}$  an acute 30-60 min ACTH stimulation test is performed. Detailed test results will be discussed in the sections of the chapter concerning NC-CAH.

**Prolactin** is a pituitary hormone, discussed in Section 8. of this chapter. Some PCOS women have an elevated prolactin level, typically falling within 25-40  $\mu\text{g/l}$ .

**Thyrotropin (TRH)** should be determined in the blood as a routine test of the pituitary thyroid axis. PCOS women usually have normal TSH levels (0.4-3.8 IU/l).

**Anti-Müllerian hormone (AMH)**, which is produced by ovarian granulosa cells in women in reproductive age. Plasma levels of AMH in women with PCOS are significantly higher than in healthy subjects. In PCOS women the average plasma level of AMH is 10.5 ( $\pm 3.6$ )  $\mu\text{g/l}$ , and is 5 times higher than in healthy women of comparable age. Interestingly, the progressive decrease of hormone levels with age is slower in women with PCOS than in healthy controls. This may suggest a larger ovarian reserve in women with PCOS (Skalba P & Cygal A. 2011) (Fig. 5).

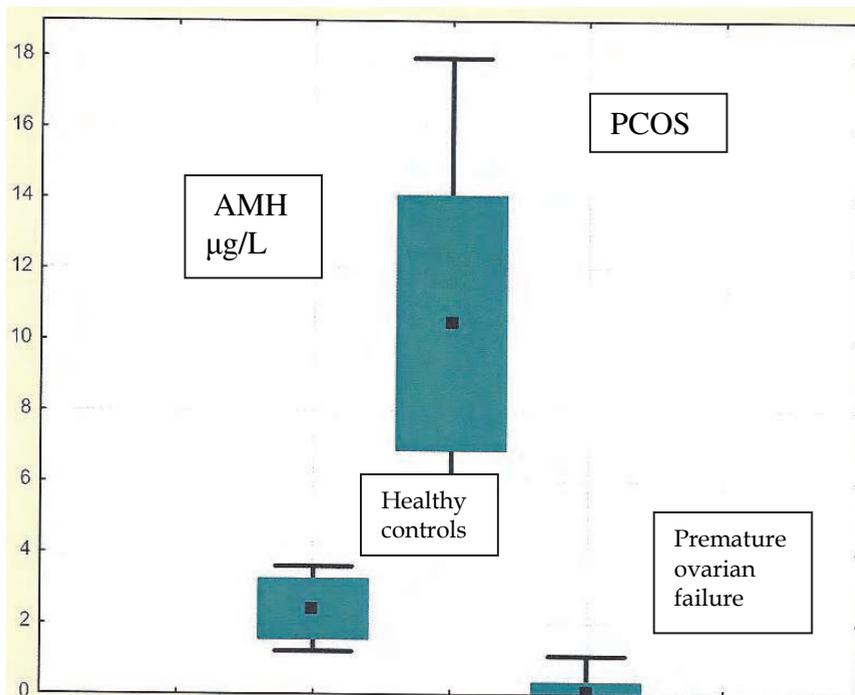


Fig. 5. AMH plasma level in healthy controls and women with PCOS and premature ovarian failure.

**Insulin and glucose.** PCOS is often accompanied by hyperinsulinism and insulin resistance, as mentioned above. Most PCOS women should have a fasting plasma glucose test and oral glucose tolerance test (OGTT). Both tests allow one to identify risk factors for insulin resistance and diabetes. For the precise diagnosis of insulin resistance, the glycemic clamp test is used. However, this method is very cumbersome and should be reserved for research purposes. The level of plasma fasting insulin is highly variable (15-25%). In women of normal weight it falls within the range of 5-15  $\mu\text{IU/ml}$ . Simple tests of sufficient specificity allowing for assessment of insulin resistance are the following factors: glucose/insulin, HOMA and QUICKI. All results are based on determinations of fasting glucose and insulin. The quantitative insulin sensitivity check index (QUICKI) is calculated from the mathematical formula:

$$\text{QUICKI} = 1 / (\log(\text{fasting glucose [mg/dl]}) + \log(\text{fasting insulin [\mu IU/ml]}))$$

A value less than 0.357 demonstrates insulin resistance.

Homeostasis model assessment (HOMA) is calculated from the mathematical formula:

$$\text{HOMA} = (\text{fasting glucose [mmol/l]} \cdot (\text{fasting insulin [\mu IU/ml]}) \cdot 22.5$$

A factor value greater than 2.5 indicates insulin resistance.

The fasting glucose-insulin ratio is simple to calculate, but also the least sensitive. The factor is calculated from the mathematical formula:

$$G/I = \text{fasting glucose (mg/dl)} / \text{fasting insulin (\mu IU/ml)}$$

An index value below 4.5 indicates reduced insulin resistance.

### 10.5 Clinical significance of obesity in PCOS

Compounds of obesity with androgen excess have already been discussed above in the section "Clinical features of androgen excess patients". It is estimated that nearly half of women with PCOS are obese. Obese PCOS women had a greater prevalence of hirsutism (73% compared with 56%) and menstrual disorders than non-obese subjects. Obesity causes changes in metabolism, including insulin resistance, glucose intolerance and metabolic syndrome. The concentration of total testosterone and androstenedione in the serum is similar in the two subgroups but SHBG concentration is significantly lower, and free testosterone levels higher, in obese PCOS women. In addition, concentration of androsterone glucuronide, a marker of peripheral  $5\alpha$ -reductase activity, is higher in obese PCOS women than in non-obese ones. Such observations may suggest impaired bio-availability of androgens to peripheral tissues and enhanced activity of  $5\alpha$ -reductase in obese subjects (Kiddy et al., 1990).

Obese women with PCOS are less likely to become pregnant. In addition, compared to normal-weight women, obese PCOS women may have lower ovulatory responses to pulsatile GnRH administration and lower pregnancy rates after gonadotropin administration (Pasquali et al., 2007).

Low birth weight modifies the relationship between insulin resistance and PCOS and seems to increase the risk of developing PCOS. Diet composition, eating disorders, and psychological stress seem to be related to the syndrome, even if no causal link has been clearly demonstrated. Intriguingly, obesity has an important pathophysiological impact on PCOS. There is some evidence that the pathogenetic factors involved in determining hyperandrogenism and metabolic abnormalities may differ somewhat between obese and lean PCOS women. In women with PCOS there were found elevated levels of these markers of inflammation, such as C-reactive protein, fibrinogen, IL-6, TNF- $\alpha$  and IL-18. Despite

reports that chronic inflammation of moderate intensity could have a role in the development of PCOS, it seems that it is secondary to obesity.

Epidemiological studies indicate that women with PCOS are at increased risk of developing cardiovascular disease. A fourfold increased risk of cardiovascular events was found in women with this syndrome (Carmina & Lobo, 1999; Chang et al., 2009 b).

### **10.6 Ovarian hyperthecosis**

Hyperthecosis refers to an unusual conditions in which the ovary contains nests of luteinized theca cells scattered throughout the stroma. The extent of theca cell involvement may vary from minimal to extensive. Severe hyperthecosis may be accompanied by extensive and dense fibroblast growth that results in an enlarged ovary of extremely firm texture. Morphology of the ovaries is therefore different from the classic PCOS, but this syndrome is considered to be a variety of PCOS, because its primary symptom is hyperandrogenism. Ovarian stromal hyperthecosis has variable sonographic features. Most commonly the affected ovaries are either normal or slightly enlarged. A solid mass may infrequently be visible, and PCOS changes may coexist with ovarian hyperthecosis. A possible association of hyperthecosis ovary with fibrothecoma was also noted (Brown, 2009). In this disorder, the cells that produce androgens are likely to be hypersensitive to the action of LH, because the plasma level of LH is generally normal, with high levels of androgens. Androgen excess causes severe hirsutism, insulin resistance and sometimes acanthosis nigricans and clitoromegaly. Androgen production may be resistant to oral contraceptive therapy, but administration of GnRH analogs causes it to decrease (Chang , 2009 a). In ovarian hyperthecosis the suggested treatment is ovarian wedge resection, although this method has already been eliminated as a means of treatment with classical PCOS.

## **11. Hyperandrogenic insulin resistance-acanthosis nigricans syndrome (HAIR-AN)**

Hyperandrogenism, insulin resistance and acanthosis nigricans constitute HAIR-AN syndrome. It is estimated that this syndrome occurs in 1-3% of women with hyperandrogenism, often in black women and women with visceral obesity and type 2 diabetes. According to the large Azziz (2004 a) studies, already cited, HAIR-AN prevalence is 3.2% of the androgen excess population.

Each of these components of HAIR-AN syndrome may also occur in women with polycystic ovary syndrome. Acanthosis nigricans is a focal hyperkeratotic, mostly gray-brown, rarely black, hyperpigmentation and papillary hyperplasia of the skin. It is usually located in the vicinity of the neck, axilla, elbows, knees and groin, but may also affect the navel and the anus, and even, in rare cases, the entire skin. These changes result from prolonged exposure to high concentrations of insulin on keratinocytes (Fig. 6).

Treatment in these cases is difficult. It is logical to use drugs that improve insulin resistance, but a randomized study of 12-month treatment with metformin or rosiglitazone showed no effect on the severity of acanthosis nigricans (Palomba et al., 2009).

## **12. Idiopathic hirsutism**

Idiopathic hirsutism (spontaneous, simple, peripheral) is hirsutism which is not accompanied by anovulation or menstrual disturbances, and serum androgen levels are



Fig. 6. 35-year-old woman diagnosed with HAIR-AN syndrome. Acanthosis nigricans in axilla and neck.

normal. It occurs in 15-20% of women with hirsutism. In some cases idiopathic hirsutism was found in a family. The pathogenesis of this type of hirsutism is believed to involve the role of increased activity of 5 $\alpha$ -reductase in the skin, excessive sensitivity of androgen receptors to these hormones, and local effects of IGF-1, insulin, glucocorticoids, thyroid hormones and estrogen. In accordance with the recommendations of the Endocrine Society Clinical Practice Guideline Societies (Martin et al., 2008) detailed diagnosis of patients is essential in the following cases: (1). Hirsutism score is calculated as >15 points on the Ferriman and Gallwey scale. (2). Hirsutism occurs suddenly and is characterized by rapid progress. (3). Hirsutism is accompanied by at least one of the following symptoms: menstrual irregularities, infertility, central obesity, acanthosis nigricans, or clitoromegaly. Idiopathic hirsutism does not require medication, although if it is burdensome for the patient either pharmacological therapy or direct hair removal methods are recommended. For women who decide on treatment of hair removal, laser depilation is recommended (photoepilation), which can be further enhanced with the use of eflornithine cream (Martin et al., 2008).

### 13. Treatment of androgen excess

Appropriate and safe treatment depends on correct diagnosis of the cause of androgen excess. Such life-threatening diseases as ovarian and adrenal malignancy or Cushing syndrome need definitive treatment regardless of symptoms. Other more common disorders, such as PCOS, require treatment adapted to current needs, preferences and phenotype of the patient. Women with virilization require medical treatment, regardless of the identified cause, because of the dramatic and often irreversible cosmetic consequences and their psychological well-being (Abdel-Rahman & Hurd, 2010). The patient should be made aware that treatment requires prolonged and regular contact with a medical specialist. In adolescent girls the biggest problems associated with PCOS are oligo/amenorrhea, acne and hirsutism.

These patients most often respond to *oral contraceptives* (OCs). Both the estrogen and progestin components of OCs reduce androgen production by the ovary and adrenal glands. The estrogens increase SHBG production by the liver, and together with progestin work centrally by inhibiting pulsatile GnRH secretion. In addition, OCs containing the progestin drospirenone (17 $\alpha$ -spironolactone derivate) block the androgen receptor.

For young patients who are overweight or obese, and who currently do not use contraception, insulin sensitizers may be proposed. *Metformin* is an oral antidiabetic drug that works by several mechanisms, including suppression of hepatic gluconeogenesis and gastrointestinal glucose absorption, and enhancement of insulin sensitivity, peripheral glucose uptake, and fatty acid oxidation (Tan et al., 2007). Metformin treatment of various symptoms of PCOS is the subject of numerous well-documented clinical studies. Currently metformin is commonly used to treat PCOS. It should be used as the first-choice agent in ovulation induction in PCOS women with insulin resistance (Palomba et al., 2009). Metformin freely crosses the placenta, resulting in exposure of the fetus to metformin therapeutic concentrations (Elliott et al., 1997).

According to experts, the use of metformin during pregnancy in PCOS women with previous miscarriage is safe and effective in reducing the rate of miscarriages (Glueck & Wang, 2007).

Metformin is indicated in patients over 10 years old, and the extended-release preparation is indicated in those over the age of 17 years (Palomba et al. 2009). It is believed that a dose of 1500-1700 mg/day is the optimal dose for induction of ovulation in PCOS women. Extremely variable target doses of 1500 to 2550 mg/day have been proposed. To minimize the drug-related adverse effects, metformin should be taken on an empty stomach, starting with a low dosage and gradually increasing over a period of 4-6 weeks. Nestler (2008) suggested administering immediate-release metformin initially at a low dose at meals, and increasing to the dose of 1000 mg twice daily.

Metformin is generally a well-tolerated drug. The most common side effect with metformin is gastrointestinal distress, which occurs in approximately 30% of patients taking metformin, limiting the compliance to treatment.

The list of gastrointestinal disorders consists of: abdominal discomfort, bloating, constipation, diarrhea, nausea and vomiting. Adverse events range from 3.3% (anovulatory bleeding) to 66% (nausea). The potential for serious side effects is estimated at 1%. Severe side effects of metformin treatment, such as lactic acidosis, can also be associated with high doses of metformin (higher than 3000 mg/d). Lactic acidosis is a rare complication of metformin administration (5.1 cases per 100 000 patient-years), although when it occurs, mortality of 50% has been observed (Palomba et al., 2009). The risk of occurrence of this severe complication increases in patients with hepatic or renal impairment, cardiac or respiratory insufficiency, severe infection, or alcoholism.

Most clinical studies indicate significant efficacy of metformin in the treatment of menstrual disorders. It is estimated that regular menstrual cycles and ovulation occur in between 35% and 90% of those treated with metformin. A meta-analysis comparing the effectiveness of PCOS treatment showed that metformin is less effective than OCs in improving the menstrual pattern (Costello et al., 2007). Effects of metformin compared with OCs are greater in the lowering of insulin and triglyceride levels but probably not in the cases of hirsutism and acne. Metformin treatment reduces the level of free testosterone, possibly due to the up-regulation of circulating levels of SHBG caused by improved insulin sensitivity, but there was not a significant treatment effect on total testosterone. It is therefore assumed that the effect of metformin on biochemical hyperandrogenism and its efficacy for clinical manifestation of hyperandrogenism are inconsistent (Palomba et al., 2009).

Other insulin-sensitizing agents include thiazolidinediones. The use of *troglistazone* at a dose of 600 mg/daily increased the ovulation rate, and reduced circulating insulin concentrations and the insulin response to an oral glucose challenge. There was also a decrease in

circulating free testosterone concentrations and a rise in SHBG. Hepatic side effects were reported for troglitazone treatment. It was also found that *rosiglitazone* therapy improves insulin resistance and glucose tolerance in obese women with PCOS, decreases ovarian androgen production and hyperinsulinism, and short-term therapy helps restore spontaneous ovulation (Rautio et al., 2006; Sepilian, & Nagamani, 2005). Initial studies seemed to indicate that the treatment described above with the new insulin-sensitizing agents offers a new perspective of treatment for overweight anovulatory women with PCOS. But unfortunately, serious side effects, causing liver damage and increased risk of myocardial infarction, prevented the introduction of these drugs to the set of therapeutic agents in PCOS.

It should be emphasized that patients with symptoms related to PCOS increasingly demand treatment with metformin. A consensus of international experts (Thessaloniki, 2008) described the position of metformin in the treatment of infertility. The consensus is summarized in the following four points: (1) At present use of metformin in PCOS should be restricted to patients with glucose intolerance. (2) The decision about continuing insulin sensitizers during pregnancy in women with glucose intolerance should be left to obstetricians providing care and based on a careful evaluation of risk and benefits. (3) Metformin alone is less effective than clomifene citrate in inducing ovulation in women with PCOS. (4) There seems to be an advantage to adding metformin to clomifene citrate in women with PCOS. It should be noted that PCOS women treated with metformin are receiving treatment for an unlicensed indication. Therefore, *clinicians must counsel women appropriately before the initiation of metformin therapy* (Harborne et al., 2003).

*Anti-androgens* are another group of agents used as a first line therapy for hirsutism. However, the teratogenic potential of these drugs means that they should be used in conjunction with adequate contraception in women of reproductive age.

*Spironolactone*, an aldosterone antagonist, competes with testosterone and dihydrotestosterone at the androgen receptor. Although it primarily acts as a potassium-sparing diuretic, a dose of 50-200 mg per day will reduce facial hair growth in most patients after 6 cycles of treatment. Patients with hirsutism who take OCs with added spironolactone for 6 months achieve better results in reducing hirsutism. The drug is not devoid of side effects such as uterine bleeding, mastodynia, hair loss and fatigue. These symptoms do not occur often (less than 15% of patients).

A derivative of 17 $\alpha$ -spironolactone is *drospirenone*, having drug action as an anti-androgen, anti-mineralocorticoid and progestin. Drospirenone has a high affinity for the progesterone and mineralocorticoid receptors and a low affinity for the androgen receptor. The drug is used in the contraceptive pill with 20 mg and 30 mg of ethinylestradiol. OCs with drospirenone are recommended for overweight PCOS women, and in the treatment of premenstrual syndrome.

Neither of the drugs mentioned above should be used in women with impaired renal function. During treatment, periodic checks of electrolyte levels, especially potassium, should be performed.

*Cyproterone acetate* is an anti-androgen as well as a progestin. The drug has strong progestational and anti-gonadotropic activity and is also a weak glucocorticoid. There is evidence that the drug inhibits the activity of 5- $\alpha$  reductase in the skin. So cyproterone acetate has an anti-androgenic effect both centrally and peripherally. The drug can be used in women with hyperandrogenism in doses ranging from 25 to 100 mg/day. It is also

available in OCs as cyproterone acetate (2 mg) with ethinyl estradiol (35 µg). This drug is not currently available in the U.S. but in Europe OCs with cyproterone acetate have been widely used for many months in young women with hirsutism and acne. In more severe cases of these disorders cyproterone acetate can be used in a so-called reverse cycle. The reverse cycle is to add 25 or 50 mg of cyproterone acetate in the first 10 days of a 21-day cycle of application of OCs. Treatment should be discontinued for about 3 months before becoming pregnant.

*Flutamide* is an anti-androgen used for treatment of prostate cancer. Flutamide is very effective in treating hirsutism, but it is associated with frequent side effects and low long-term compliance. Hepatic cell damage, the major complication of flutamide, may be fatal (Abdel-Rahman, 2010). Consequently the drug is rarely used, is considered a second-line treatment, and is not approved by the FDA for treatment of hirsutism.

*Finasteride* selectively inhibits type 2 isoenzyme of 5- $\alpha$ -reductase to prevent the formation of 5- $\alpha$ -dihydrotestosterone. The drug is intended to treat benign prostatic hyperplasia and male pattern baldness. The FDA has not approved finasteride for treatment of hirsutism.

#### 14. Infertility treatment related to PCOS

Before any intervention is initiated, preconceptional counseling should be provided emphasizing the importance of life style, especially weight reduction and exercise in overweight women, smoking and alcohol consumption.

According to the Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2007) first-line treatment for ovulation induction remains the anti-estrogen clomifene citrate (CC). The mechanism of drug action is not completely understood, but it is assumed that it increases the secretion of FSH. There are no specific criteria for PCOS women who have normal FSH and estradiol levels. Note also that in women with an increased ovarian volume and serious hyperandrogenism the response to CC is worse. Therefore, most clinicians recommend reducing plasma androgen levels before the start of ovulation stimulation. Patients with high BMI and older age also respond less well to CC, which is why their treatment with gonadotropins is justifiable.

The recommended dose is 50-150 mg of CC per day. The size of the initial dose is 50 or 100 mg/day depending on body weight. The maximum daily dose is 150 mg; higher doses do not increase efficacy. It is given for 5 days, starting from cycle day 2-5. If ovulation cannot be achieved within 6 months, further treatment is considered to be ineffective.

Hot flushes and visual complaints are well-recognized side effects during CC treatment, but they are rare, and the drug is considered safe. Metformin alone and in combination with CC were discussed above.

Recommended second-line treatment intervention, should CC fail to result in pregnancy, is either exogenous gonadotropin or laparoscopic ovarian surgery (LOS). Taking into account the risk of ovarian hyperstimulation syndrome (OHSS) in women with PCOS, low-dose protocols (37.5-75 IU FSH/day) are recommended. Currently two low-dose regimens are used:

1. Step-up regimens are based on the principle of stepwise increases in FSH supply to determine the FSH threshold for follicular development. If after use and treatment for a week there is no follicle increase, the dose should be increased.
2. The step-down regimen is designed to achieve the FSH threshold through a loading dose of FSH with subsequent stepwise reduction as soon as follicular development is observed on ultrasound.

It was proved that the step-up regimen is safer in terms of monofollicular development. FSH treatment must be monitored, by serial ovarian ultrasound, and estradiol concentrations in the blood. Measurement of circulating estradiol levels has been used to cancel ovulation induction. Overall, ovulation induction (representing CC and FSH) is reported to be highly effective, with a cumulative singleton live birth rate of 72% (Thessaloniki Consensus, 2008).

The main indication for LOS is CC resistance in women with anovulatory PCOS. LOS also may be recommended for patients with hypersecretion of LH and patients who have experienced OHSS. Commonly employed methods for LOS include monopolar electrocautery (diathermy) and laser (ovarian drilling). Ovarian wedge resection is now rarely performed. A laser fiber or electrosurgical needle is used to puncture the ovary. Most authors use between four and ten punctures; however, more punctures have been associated with premature ovarian failure (Malkawi et al., 2003). There can be found in the literature very optimistic opinions, evaluating the efficacy of LOS obtained in 40-60% of pregnancies. However, according to experts, in 50% of LOS-treated patients, adjuvant therapy is required. In addition, five studies compared the effectiveness of LOS with that of gonadotropins for women with CC-resistant PCOS and did not find a difference in the ongoing pregnancy rate (Thessaloniki Consensus, 2008).

The recommended third-line treatment is in vitro fertilization.

## 15. Nonclassic congenital adrenal hyperplasia

One of the frequent causes of hyperandrogenism in young women is nonclassic congenital adrenal hyperplasia (NC-CAH). Whereas 21-hydroxylase (21-OH) deficiency accounts for the vast majority of NC-CAH, deficiency in 11- $\beta$ -hydroxylase (11-OH) and 3- $\beta$ -hydroxysteroid dehydrogenase (3- $\beta$ -HSD) may result in the disorder (Azziz et al., 1994). The 21-OH genes are duplicated genes located on chromosome 6. The CYP21 gene (also designated CYP21B) is active, whereas CYP21A is inactive due to various nucleotide insertion, deletion, and point mutations. Approximately 90% of NC-CAH patients have one or more CYP21 mutations. Whereas NC-CAH is considered a homozygous recessive disorder, in most cases the same mutation does not affect both CYP21 alleles, and many patients have one mild and one severe CYP21 mutation (Azziz et al., 1994). Prevalent allelic mutations and genotypes were found to vary significantly among ethnic groups. There are ethnic-specific mutations in the CYP21A2 gene (for example, the mutation V281L is prevalent in Ashkenazi Jews). The phenotype of patients and severity of endocrine disorders depends on the specific genotype of patients, but assessment of the genotype is not possible on the basis of clinical manifestations (Bided et al., 2009).

### 15.1 Prevalence, clinical and biochemical features

NC-CAH appears to affect 1-2% of Caucasian hyperandrogenic women. In the Gynecological-Endocrinology Department of the Medical University of Silesia in the years 2003-2009, 2553 hyperandrogenic patients were hospitalized, and in 1.2% of them NC-CAH was identified (Franik & Skalba, 2011). It is estimated that in the populations of Central European countries, including Poland, and in the U.S. the incidence of NC-CAH is 1-2%. In contrast, studies from France, Italy, Croatia, and Canada have indicated prevalence of 3% to 6%, and studies from Israel, India and Jordan found prevalence of 6% to 10% (Romaguera, 2000). NC-CAH occurs much more frequently in the population of Ashkenazi Jews, Iranians and Yupik-speaking Eskimos of Western Alaska.

The symptoms of hyperandrogenism most often manifest peripubertally, frequently coinciding with the onset of adrenarche. In contrast, patients with classic adrenal hyperplasia have clinical features at birth or shortly thereafter. NC-CAH patients may exhibit short stature, premature development of pubic hair, insulin resistance and acne. Androgenic symptoms are usually mild, but hirsutism is often more pronounced (Franik & Skalba, 2011). However, clitoromegaly (but not true genital ambiguity), male habitus and temporal baldness are infrequent findings (Fig. 7). Menstrual disorders (oligo-/amenorrhea) and infertility occur in most patients. Ultrasonographic examination reveals PCO in the ovaries in about one third of patients. It should be stressed that symptoms of NC-CAH are very similar to those of PCOS, and on the basis of the clinical presentation patients suffering from these two disorders cannot be distinguished. As with other hyperandrogenic disorders, it is probable that NC-CAH is a progressive disorder, with symptoms becoming worse with age. Some women with NC-CAH may not show obvious symptoms. The disease is detected in them unintentionally, and it is also possible that it is not disclosed at all.



Fig. 7. 18-year-old woman diagnosed with NC-CAH with clitoromegaly.

Circulating testosterone and DHEAS are not different from ovarian hyperandrogenism, and DHEAS levels are often normal. It is important that circulating androstenedione is usually higher than in PCOS women, but the overlap between the two populations is too great to be of use as an effective marker. Patients with NC-CAH do not usually have an abnormally elevated LH/FSH ratio, although nor do many patients with ovarian hyperandrogenism (Azziz et al., 1994). It is interesting that the plasma level of estradiol in NC-CAH women is higher than in PCOS women, although the mechanism of increased production of estradiol in the ovaries in this disorder is not understood (Franik & Skalba, 2011). NC-CAH patients do not generally show ACTH oversecretion and cortisol deficiency (Raquel et al., 2000).

The standard diagnostic test for NC-CAH is the ACTH stimulation test. The test should be performed in patients with features of hyperandrogenism, when the 17OHP plasma concentration is above 1.7 µg/l. A blood sample for testing must be taken in the early morning in the early days of the menstrual cycle. The test involves intravenous administration of 0.25 mg of ACTH (for example, Synacthen), and collecting blood samples 30 minutes and 60 minutes after injection. In all blood samples 17OHP is determined. If the concentration of the hormone prior to administration of ACTH, or 60 minutes after injection, is equal to or greater than 10 µg/l, NC-CAH should be diagnosed.

### 15.2 Treatment of NC-CAH

The primary goal of treatment is to reduce hyperandrogenism. This applies to both glucocorticoids as well as anti-androgens. In special cases, a combination of the two groups of drugs may be used. Generally, very low doses of dexamethasone are needed (0.25-0.5 mg nightly). Anti-androgens were described in the above section of the chapter. In subfertile NC-CAH women, ovulatory function may be restored by dexamethasone treatment. In some patients, especially those who have symptoms of PCO, dexamethasone treatment may not be sufficient. For them, there are other ways to stimulate ovulation. In fact, many NC-CAH patients become pregnant without special treatment. During pregnancy in patients with NC-CAH "in utero" virilization may occur because of CAH in the fetus. Such a situation may arise if the father is a carrier for CAH, and the mother is a compound heterozygote. The risk of being a carrier is between 1/20 and 1/50 in the general Caucasian population. In pregnant NC-CAH cases, where the father's carrier status is not known, performance of prenatal testing and possible prenatal administration of dexamethasone should be considered.

### 16. Conclusion

The pattern of normal menstrual cycles is achieved through functional integration of stimulatory and inhibitory signals from the hypothalamus, pituitary and ovary. The important menstrual cycle disturbances concern primary or secondary amenorrhea. Disorders of the hypothalamic-pituitary-ovary axis arise from genetic defects, functional disorders and organic changes. Disorder treatment includes pharmacological, surgical and psychological methods. Improved treatment results should be sought in the development of research on the nature of the mechanisms of hormonal disorders.

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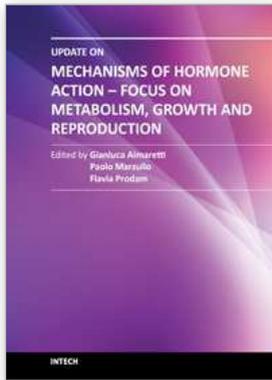
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## **Update on Mechanisms of Hormone Action - Focus on Metabolism, Growth and Reproduction**

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The purpose of the present volume is to focus on more recent aspects of the complex regulation of hormonal action, in particular in 3 different hot fields: metabolism, growth and reproduction. Modern approaches to the physiology and pathology of endocrine glands are based on cellular and molecular investigation of genes, peptide, hormones, protein cascade at different levels. In all of the chapters in the book all, or at least some, of these aspects are described in order to increase the endocrine knowledge.

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