Endocrine Gland Disorder-Related Amenorrhoea

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7.1 Introduction

Amenorrhoea is the absence or cessation of menstruation. Amenorrhoea is conventionally divided into primary and secondary amenorrhoea. In this chapter, we focus on secondary amenorrhoea, which means that menstruation starts but then stops. The endocrine gland disorders play a crucial role in menstrual irregularity and in amenorrhoea. The menstrual cycle includes ovarian and endometrial cycles in which the cyclic response to the hormone production from the hypothalamus, pituitary, thyroid as well as adrenals leads to the occurrence of menstrual cycle. We focus on the hormonal changes and results of menstrual disturbances, which have been observed in pituitary, thyroid and adrenal disorders.

7.2 Pituitary Tumours

Pituitary adenomas are the most common reason for hypothalamic-pituitary system disorders, the etiopathogenesis of which is complex and not fully clarified. Adenomas frequently result in hyperpituitarism; hypopituitarism is observed rarely.

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Hyperpituitarism is usually accompanied by prolactin (PRL) excessive release due to microadenoma (tumour diameter smaller than 10 mm) or macroadenoma (tumour diameter bigger than 10 mm) presence. Growth hormone (GH) release is observed less frequently.

7.2.1 Hyperprolactinaemia

Hyperprolactinaemia is prolactin excessive release, which physiologically accompanies pregnancy, lactation or physical exertion. Its pathological character is observed in pituitary gland adenoma in patients with hypothalamic pituitary system disorders or liver or kidney failure or as drugs' side effect. Prolactinomas are the most common pituitary tumours, and they constitute up to 40% of all tumours. They prevail more often in females than in males: 30/100,000 vs. 10/100,000.

Hyperprolactinaemia increases hypothalamus endorphin neuron activity, resulting in gonadotropin-releasing hormone (GnRH) pulse impairment [1]. As a consequence, pituitary gonadotropin-luteinising hormone (LH) as well as follicle-stimulating hormone (FSH) release is disturbed, too. In females, the Graafian follicle development as well as ovaries' endocrine activity are inhibited, which provokes oestradiol and progesterone deficiency. In females, hyperprolactinaemia results in galactorrhoea. Corpus luteum insufficiency with preserved ovary oestrogen function may result in mastodynia. The most common symptom of female hyperprolactinaemia is menstrual cycle disturbances. Along with prolactin concentration growth, luteal phase deficiency is observed followed by anovulation, scarce and rare menstruation and absolute amenorrhoea called "secondary amenorrhoea". In 25% of hyperprolactinaemia cases, macroprolactin (big-big prolactin) predominant form is observed, and it is prolactin bound with anti-PRL immunoglobulin G (IgG). In practice, in macroprolactinaemia patients, hyperprolactinaemia with normal ovulation cycle is diagnosed.

Prolactinoma diagnosis is based upon amenorrhoea-galactorrhoea syndrome recognition, increased prolactin concentration (over 150.0 microg/L) definition as well as magnetic resonance imaging (MRI) visualisation of pituitary adenoma. Hyperprolactinaemia of 25.0–150.0 microg/L is a frequent and difficult diagnostic problem of functional or iatrogenic origin. In such cases, the goal of treatment is prolactin concentration normalisation and gonad normal function restoration. As a result, menstruation abnormalities and galactorrhoea regress, libido and fertility are restored and the risk of osteoporosis is limited.

Drugs of choice are dopamine agonists, which not only inhibit PRL secretion but also provoke tumour regression. The oldest (40 years on the stock), the cheapest and the most effective drug is ergot derivative—bromocriptine, applied in doses dependent on PRL level. With available tablets (2.5 mg), administration starts with 2.5 mg daily at night, and after 5 days, the dose is gradually increased by ½ tablet. After next 5 days, it is increased by another ½ tablet up to where therapeutic dose is finally achieved. Therapeutic dose depends on PRL level, and it amounts to 2.5–30.0 mg/24 h due to side effects such as blood pressure orthostatic decrease,

nausea, vomiting constipation and drowsiness. As its activity persists for 8–12 h, administration twice a day is recommended.

Another drug is quinagolide, the activity of which persists for 24 h; daily dose is dependent on PRL level and amounts to 75–600 microg/24 h. The risk of side effects is smaller than in the case of bromocriptine. Cabergoline is a drug of the longest duration. It can be administered once or twice a week in a dose dependent on PRL concentration, which is 0.5–3.0 mg per week. It reveals the biggest efficacy and the smallest number of side effects. However, the risk of cardiac valve fibrosis should be taken into account with cabergoline's prolonged administration. This drug application provides prolactin concentration normalisation in 90–95% of patients. In 90% of patients, it provokes tumour size reduction. Operative treatment is indicated in cases of pharmacotherapy intolerance or resistance. Its results depend upon tumour size and location.

7.2.2 Acromegaly

Acromegaly is a chronic disease resulting from growth hormone excessive production and most often, in 99%, it is caused by pituitary adenoma autonomic secretion. Only sporadically, it results from excessive release of growth hormone by neuroendocrine neoplasms. Macroadenomas (diameter bigger than 10 mm) constitute about 80% of all adenomas. Smaller tumours are rare. Majority of tumours (about ¾) are built of somatotropic cells. The remaining ones also release prolactin due to mammotropic cells' presence, and somatotropic and mammotropic mixed form is rather rare. Excessive release of growth hormone results in patient's appearance change such as palms, feet and facial structure enlargement as well as soft tissues. Hyperplasia of bones and internal organs may occur, and many other complications including cardiovascular system are the reason for increased mortality. The possible manifestation on menstrual cycle due to the higher levels of prolactin and oestrogen deficiency was observed in acromegaly. Kaltsas et al.'s [2] study showed that 62% of patients with acromegaly experienced amenorrhoea, 15% had oligomenorrhoea and 4% had polymenorrhoea. Data from the multi-centre acromegaly registry reported that hypogonadism was observed in more than half of the women with acromegaly [3].

Diagnosis of active acromegaly is carried out on the basis of characteristic clinical symptoms and signs, hormonal disturbances as well as presence of pituitary tumour found in MRI. In hormonal diagnosis, if insulin-like growth factor-1 (IGF-1) values are increased, it is recommended to perform an oral glucose tolerance test (OGTT) after administration of 75 g of glucose. The diagnosis is confirmed by an increased IGF-1 concentration and no suppression of GH secretion below 0.4 microg/L (ng/mL) in OGTT. Random GH level below 1.0 microg/L allows the exclusion of active acromegaly [4]. Operative treatment is recommended, but if it does not bring GH concentration and IGF-1 normalisation, somatostatin analogue therapy should be introduced.

7.2.3 Cushing's Disease

Cushing's disease is a hypercortisolaemia condition induced by adrenocorticotropic hormone (ACTH) excessive release (ACTH-dependent Cushing's syndrome). Most often, in 95%, it is caused by ACTH-releasing pituitary isolated adenoma. In about 5% of cases, primary disturbances of hypothalamic corticoliberin or vasopressin release are probably related to corticotropic cell hyperplasia. Besides, Cushing's disease can be a component of multiple endocrine neoplasia type 1 syndrome (MEN1). Clinically, it is characteristic for reddened and round face (moon-shaped face), red skin stretches, neck and corpus fat deposition (central obesity), atrophy of limb muscles, hypertension, diabetes and osteoporosis. In turn, Cushing's syndrome (non-ACTH-dependent Cushing's syndrome) is every hypercortisolaemia condition not provoked by ACTH release and also caused by adrenal carcinoma. In majority of Cushing's disease patients, gonad function abnormalities are observed. Hypercortisolaemia disturbs GnRH release and inhibits gonadotropin secretion. In females, it results in menstruation disturbances (oligomenorrhea, amenorrhea) in 56–80% woman affected by hypercortisolemia and infertility [1]. Menstrual irregularity seems to be most closely related to the level of serum cortisol rather than androgen level [5]. Obviously, increased ACTH release results in increased androgen production and hyperandrogenism favours seborrhoea, acne and hirsutism.

In diagnostics, 1.0 mg dexamethasone application proves to be useful in testing cortisol release inhibition. In physiological conditions, after oral administration of 1.0 mg dexamethasone dose at 11 pm, on the next day, cortisol concentration determined at 8 am is below 1.8 μg/dL (50.0 nmol/L); the Cushing's syndrome is excluded. Besides, increased cortisol concentration determined in 24-h urine collection is also very useful in a diagnostic process.

Surgical treatment of adenocarcinoma is of strategic importance in the course of the whole therapy. Steroidogenesis inhibitors should be applied in hypercortisolaemic patients before the operation. In the case of insufficient effect of the therapy, reoperation is indicated as well as adrenalectomy and radiotherapy subsequently. Inefficacy of surgical treatment may be corrected by applying pasireotide—a new somatostatin analogue, which reveals big affinity to somatostatin receptor fifth type.

7.3 Thyroid Disorders

Thyroid hormones are essential for proper development and differentiation of all cells of the human body. They affect the female reproductive organ; in combination with FSH, triiodothyronine enhances granulose cell proliferation and inhibits granulose cell apoptosis by the protein kinase B pathway. Thyroid hormone receptors are expressed in endometrium [6]. The highest level of expression of thyroid hormone receptors was found in receptive endometrium, and it proved that thyroid hormones influence endometrial function [7]. Transcripts required for thyroid hormone synthesis and metabolism such as thyroid peroxidase, thyroglobulin and 5-deiodinase type 2 were also identified in human endometrium, suggesting

possible thyroid hormone production [8]. Expression of TSH and thyroid hormone receptors was revealed in human oocytes in physiological and non-physiological methods, during in vitro fertilisation (IVF) programme, conditions indicating direct thyroid hormone action in human ovaries. Deiodinase-2 and deiodinase-3 transcripts were determined in granulosa cells, suggesting their ability to control local hormone activity through deiodination of T4 to either T3 or, to a lesser extent, reverse T3 [6, 9, 10].

Leukaemia inhibitory factor (LIF) is involved in the embryo implantation process and expressed in the mid-secretory endometrium. TSH significantly upregulates leukaemia inhibitory factor expression in endometrial cell cultures, which suggests a potential role of TSH in the implantation process. For that reason, we can expect reproduction disturbances in case of thyroid disorders [10].

7.3.1 Hypothyroidism

The prevalence of menstrual abnormalities reported is 25–60% in hypothyroid women compared to 10% in euthyroid women. The predominant menstrual disturbance in hypothyroid women described is oligomenorrhoea [11, 12]. Thyroid autoimmunity (TAI) is the most frequent autoimmune disorder in women of childbearing age, and it increases the risk of thyroid dysfunction. The prevalence of TAI is generally estimated at around 10% [13]. In women with elevated anti-thyroperoxidase (ATPO) antibody titres, the relative risk of female infertility is increased [14, 15].

Hypothyroidism may also lead to a diminished LH response, thereby stimulating thyrotropin-releasing hormone (TRH) secretion and increasing serum prolactin levels. As PRL impairs pulsatile secretion of GnRH, this can lead to ovulatory dysfunction [12, 15]. For that reason, in hypothyroidism, we can expect decrease of serum oestradiol and sex hormone-binding globulin (SHBG), increase of PRL and androstenedione as well as impaired GnRH secretion, resulting in menstrual irregularities and anovulation [13]. Clinical symptoms of hypothyroidism are the following: fatigue, increased sensitivity of cold, constipation, dry skin, weight gain, puffy face, muscle weakness, muscle aches, tenderness and stiffness, pain, stiffness or swelling joints, heavier-than-normal or irregular menstrual periods, secondary amenorrhoea, thinning of hair, slowed heart rate, depression and impaired memory.

Diagnosis is based on elevated serum TSH levels over 5.0 mIU/L as well as FT4 lower than 0.7 ng/dL (normal range of TSH 0.5–5.0 mIU/L, FT4 0.7–1.9 microg/dL).

The L-thyroxin is the first-choice therapy, and it proves to be very successful; hormonal changes and menstrual pattern may normalise [16].

7.3.2 Hyperthyroidism

Studies on the prevalence of subfertility in women with hyperthyroidism are limited. Majority of them are uncontrolled, retrospective and small population studies. In contrast to hypothyroidism, increased serum SHBG is characteristic for

hyperthyroidism so much that this globulin is used as a test of thyroid function, revealing tissue response to the thyroid hormone. It should be considered when levels of oestradiol and testosterone are interpreted because the total amounts are increased out of proportion to free levels. It has been published that total oestrogen levels may be two- to threefold higher in hyperthyroid women (compared to normal women) [17]. Serum LH and FSH may also be increased; mean LH levels are higher in hyperthyroid women (compared to normal women) [17–19]. It has been published that during the early follicular phase of the menstrual cycle, the LH secretion was increased in hyperthyroid women with GD, whereas the pulsatile characteristics of LH and FSH secretion did not differ in patients when compared to controls [18, 20, 21]. Serum LH levels decrease to normal after a few weeks of treatment with anti-thyroid drugs (ATD) [19]. The mechanism underlying the increase in serum LH in hyperthyroid women is as yet unclear [16].

In prepuberty girls, menstruation has been reported to be delayed [16, 17]. The primary or secondary infertility in 5.8% of hyperthyroid patients has been presented, but other prospective studies have showed the prevalence of suppressed TSH (subclinical or overt hyperthyroidism) in 2.1% compared to 3% in fertile controls [12, 14]. Despite a comparable prevalence of hyperthyroidism, suppressed TSH was more prevalent in antibody-positive compared to antibody-negative patients [14]. Recent data showed a lower prevalence of menstrual abnormalities of about 22% compared to 8% in healthy controls [22]. Clinical symptoms of hyperthyroidism are the following: (1) non-specific symptoms like tachycardia, increased sweating, nervousness, tremor and weight loss and/or (2) specific symptoms like goitre, thyroid ophthalmopathy, pretibial oedema, lower serum TSH (normal range of TSH 0.5–5.0 mIU/L), proximal myopathy, weight loss and increased TRAb titre.

For thyrotoxicosis therapy, propylthiouracil (PTU) or methimazole (MMI) is recommended. However, in the first and second trimesters of pregnancy, PTU and MHI therapies are recommended, respectively [23]. They are also not contraindication to breastfeeding in women treated for hypo- and hyperthyroidism [23].

7.4 Adrenal Gland Disorders

Non-classical congenital adrenal hyperplasia (N-CCAH) is another disorder that may influence the menstrual cycle; the most common manifestations of menstrual disorder in these patients are primary or secondary amenorrhoea and oligomenorrhoea.

7.4.1 Non-classical Congenital Adrenal Hyperplasia Due to 21 Hydroxylase Deficiency

N-CCAH due to 21-hydroxylase deficiency is one of the most common congenital autosomal diseases, and it results from CYP21A2 gene mutation. This abnormality is observed in 1–2% of androgenic females. 21-Hydroxylase deficiency causes cortisol synthesis inhibition, increased ACTH release and increased androgen

secretion, and in severe cases, it results in deoxycortisol and aldosterone deficiency. Shortage of cortisol provokes pituitary gland to release increased amounts of ACTH which, in turn, stimulates adrenal glands. 17-Hydroxyprogesterone (17-OHP) is accumulated which, due to 21-hydroxylase block, does not turn into 11-deoxycortisol and cortisol, and progesterone does not turn to 11-deoxycorticosterone. Steroids, the synthesis of which is not disturbed, are accumulated and adrenal androgens [dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), androstenedione and testosterone] are excessively released.

Clinical picture of non-classical and late-onset form of the disease is characteristic for preserving 20–50% of 21-hydroxylase activity and moderate increase of androgen synthesis. In this form of N-CCAH, symptoms develop later; they are diverse and hard to recognise. They may include premature puberty, purulent acne, preterm growth and epiphyseal plate preterm mineralisation, which finally may result in short stature. Non-classical form signs and symptoms are observed in adulthood, and they are diagnosed in females only as they reveal hirsutism, seborrhoea, temporal alopecia, clitoris enlargement, menstruation abnormalities and infertility. The disease increases the risk of metabolic syndrome. During the diagnostic process, apart from the above clinical symptoms, some other specific manifestations should be established. These are increased concentration of 17-OHP over 10.0 ng/mL, increased concentration of androgen ACTH in plasma as well as 17-ketosteroid presence in urine. Concentration of 17-OHP over 10.0 ng/mL after 60 min with ACTH intravenous stimulation confirms diagnosis of non-classical form. Increased levels of DHEA, androstenedione and testosterone are observed as well. In order to avoid the development of polycystic ovary syndrome (PCOS), oral contraceptives are administered to females with non-classical form of congenital adrenal cortex hyperplasia. In case of strong androgenisation, spironolactone or flutamide is applied. The therapy should be monitoring of 17-OHP concentration in serum. In case of females in their reproductive period who do not use contraceptives or in those during pregnancy, dexamethasone should be replaced with hydrocortisone. Dexamethasone penetrates placenta, and it can adversely affect the functioning of hypothalamic and pituitary system in normal foetuses. The drug is administered in the case of early diagnosis of CYP21A2 gene mutation in female foetuses [24].

7.4.2 Non-classical Congenital Adrenal Hyperplasia Due to 11-Beta-Hydroxylase Deficiency

Non-classical congenital hyperplasia due to 11-beta-hydroxylase deficiency results from CYP11B1 gene mutation. Absolute lack or deficiency of 11-beta-hydroxylase results in androgenisation along with cortisol deficiency and hypertension. Cortisol synthesis inhibition increases ACTH release. It results in adrenal hyperplasia and increased release of adrenal androgen, 11-deoxycorticosterone and 11-deoxycortisol.

Non-classical form is characteristic for its delayed onset of clinical symptoms. Baby girls are delivered with normal sexual organs, and only in their reproductive period, hirsutism and menstruation abnormalities (primary or secondary

amenorrhea and oligomenorrhea) may appear [1]. Premature adrenarche and puberty are also very common as well as hypocalcaemia and hypertension.

In the diagnostic period, determination of 11-deoxycortisol and 11-deoxycorticosterone in serum, DHEAS, androstenedione and testosterone proves to be useful.

In the course of the therapy, hydrocortisone application until the puberty period and dexamethasone administration afterwards may provide good effects. If hypertension still persists, spironolactone or amiloride is recommended [25].

7.4.3 Addison's Disease

Addison's disease is a rare adrenal disorder characterised by low secretion of adrenocortical hormones. Female patients with Addison's disease may experience menstrual irregularity, but there is no sufficient data regarding the type of menstrual disturbance that is mostly observed in this rare disorder [1]. If Addison's disease is suspected, blood tests are carried out to measure the serum levels of sodium, potassium and cortisol. A low sodium, high potassium or low cortisol level may indicate Addison's disease.

7.5 Conclusions

Endocrine glands (pituitary, thyroid, adrenals) play a functional role in the endocrine regulation of a woman's menstrual cycle. In the simple diagram attached, we present the basic tests to be performed if secondary amenorrhoea is present and pituitary, thyroid and adrenal abnormalities are suspected (Fig. 7.1). As a result,

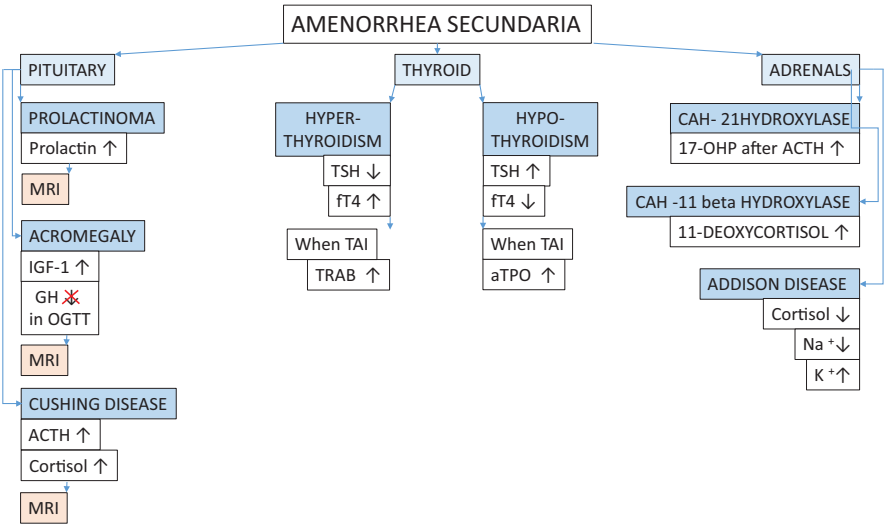

Fig. 7.1 Basic tests to be performed if secondary amenorrhoea is present and pituitary, thyroid and adrenal abnormalities are suspected

endocrine disorders are the triggers of onset of menstrual disturbance across the reproductive lifespan of women. Further studies are highly needed for better clarification of the underlying pathways of the association between endocrine disorders and menstrual cycle.

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