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WHAT IS THE HEALTH RISK ASSOCIATED WITH AMENORRHEA?

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SUMMARY – Amenorrhea is one of the most common symptoms in the woman's health pathology. It can be caused by anatomical defects of the outflow tract (uterus, cervix, vagina), thus being in the gynecologist's domain, or can be observed in gonadal dysgenesis (Turner's syndrome), hypopituitarism (Sheehan's syndrome), prolactin-secreting pituitary tumors, Cushing's syndrome, hyperthyroidism, stress, anorexia nervosa, polycystic ovaries, and in women upon discontinuation of oral contraceptives, especially if they have a history of prior menstrual irregularities. Endocrine abnormalities may also be due to changes in target tissue responses to hormones. These disorders can occur by a variety of mechanisms. Endocrine glands may be injured or destroyed by neoplasia, infections, hemorrhage, autoimmune disorders, and many other causes. Menopause, pregnancy and lactation are the most common causes of ammenorrhea. Hypothalamic lesions resulting in impaired secretion of releasing hormones may manifest themselves by pituitary dysfunction, which in turn leads to functional abnormalities of its various target organs. Extraglandular disorders can result in hormone deficiency and become manifest with amenorrhea as one of the symptoms. Assessment of the patient's endocrine status relies on the findings from the history, physical examination and laboratory testing. The latter can include measurement of hormone levels of their metabolites in plasma or urine either in basal state or in response to provocative testing. For endocrine deficiency syndromes, hormones are generally administered to counteract the deficiency. In hormone excess syndromes, a variety of approaches have been used. Hyperfunctioning tumors are removed when possible, and sometimes hyperplastic glands are extirpated. In other cases, drugs are given to block hormone production. Menopause related osteoporosis is the leading health problem associated with amenorrhea and should be treated as early as possible, i.e. from the beginning of the period of menses disappearance.

Key words: *Amenorrhea, etiology; Amenorrhea, diagnosis; Amenorrhea, complications; Osteoporosis, etiology; Osteoporosis, prevention and control*

Introduction

Various physical, chemical and physiological stressors can provoke the cessation of menses. The most common are normal causes such as pregnancy, lactation and natural menopause. The genetic pattern is unknown. The incidence of primary amenorrhea is 0.3%, and of secondary amenorrhea 3.3%. An attempt has been made herewith to explain the reasons that lead to amenorrhea and, which is very important, the real risk for woman's health associated with amenorrhea.

The absence of menarche by age 16 irrespective of the presence or absence of secondary sexual characteristics is termed primary amenorrhea. The cessation of menses for longer than 6 months in a patient who has previously menstruated is termed secondary amenorrhea. There are disorders that can cause both primary and secondary amenorrhea (anatomical defects of the outflow tract, ova-

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rian failure, chronic anovulation with or without the presence of estrogen), thus functional classification is preferred.

Causes of Amenorrhea

Primary amenorrhea
- imperforate hymen
- agenesis of the uterus and upper 2/3 of the vagina (müllerian agenesis)
- Turner's syndrome
- constitutional delay

Secondary amenorrhea
- physiological: menopause, pregnancy, lactation, corpus luteal cyst
- suppression of the hypothalamic-pituitary axis, post-pill amenorrhea, stress, intercurrent illness, weight loss, low body mass index
- pituitary disease: ablation of the pituitary gland, Sheehan's syndrome, prolactinoma
- uncontrolled endocrinopathies: diabetes, hypo- or hyperthyroidism
- polycystic ovarian disease (POD) (Stein-Leventhal syndrome)
- chemotherapy
- pelvic irradiation
- endometrial ablation (Asherman's syndrome)
- drug therapy: systemic steroids, danazol, GRH-RH analogs, antipsychotics, OCPs
- premature ovarian failure

Primary amenorrhea is the physiologic end of fertility in women. It is a physiologic state in the life of every woman, however, this 'physiologic disease' carries a lot of problems that are not physiologic by nature and cause considerable difficulties in a woman's life. The development of endocrinology has contributed greatly to the understanding of the very specific pathophysiologic mechanism of ovarian hormone regulation. Low estrogen and progesterone levels in menopausal women predispose to a faster development of some chronic diseases such as elevated blood pressure, atherosclerosis and osteoporosis. A low level estrogen/progesterone replacement therapy introduced on time could be the mode of protection in menopausal women.

Also, many congenital anatomical defects of the outflow tract include congenital defects of the vagina, imperforate hymen, transverse vaginal septum, cervical stenosis, intrauterine adhesions, absence of the vagina or uterus, and uterine maldevelopment. These conditions are usually diagnosed by physical examination and confirmed by demonstrating failure of bleeding following administration of estrogen plus progesterone for 21 days[1]. Pelvic ultrasonography, magnetic resonance imaging (MRI), hysterosalpingography or hysteroscopy may also be helpful in defining the defect. The causes of ovarian failure include gonadal dysgenesis, resistant ovary syndrome, and premature ovarian failure. An elevated plasma level of follicle stimulating hormone (FSH) confirms the diagnosis. Women with chronic anovulation fail to ovulate spontaneously but have the capability of ovulating with appropriate therapy. In some women with this condition, total estrogen production is adequate, but it is not secreted in a cyclic fashion. In others, estrogen production is deficient[2-4]. Women who have adequate estrogen production and demonstrate withdrawal bleeding after progesterone challenge, usually have polycystic ovarian syndrome. Other causes include hormone-secreting ovarian and adrenal tumors. Women with deficient or absent estrogen production, and thus absent withdrawal bleeding after progesterone administration usually have hypogonadotropic hypogonadism due to organic or functional disorders of the pituitary or central nervous system (CNS) such as brain tumors (especially prolactin-secreting), or primary hypopituitarism[5].

Hypothalamic hypogonadism due to hypothalamic disease can cause pituitary hyper- and/or hypofunction of a varying severity. A mild disease can cause subtle alteration of the feedback loops and timing, so that, for example, the integration of signals necessary for menstrual cycling is lost, resulting in 'hypothalamic' amenorrhea[6].

The disorders causing these conditions may be primary (congenital defects) or acquired, may be restricted to gonadotropin-releasing hormone (GnRH) or may also cause the loss of other hormones. Prepubertal lesions result in failure of the onset of puberty, or in incomplete progression of puberty if the defect is partial. The most common congenital lesion causing prepubertal GnRH deficiency is Kallman's syndrome – hyposmia or anosmia due to hypoplasia of the olfactory bulb along with absent GnRH secretion. Among females with primary amenorrhea due to GnRH deficiency, 37% were found to have associated anosmia and thus Kallman's syndrome. When 12 of these women were studied for gonadotropin pulsatile secretion, 11 had no pulsations.

Other hypothalamic lesions associated with impaired GnRH production, thus leading to hypogonadotropic

hypogonadism include craniopharyngioma, germinoma, glioma, teratoma, endodermal sinus tumors, tuberculosis, sarcoidosis, and metastatic tumors.

Craniopharyngiomas are common tumors of the hypothalamus, arising from remnants of Rathke's pouch[7]. They consist of cysts alternating with stratified squamous epithelium. Although presenting at any age, craniopharyngiomas are most common in children. They are often calcified and can therefore be visualized by conventional skull films[8]. The symptoms include headache, vomiting, visual impairments, seizures, hypopituitarism (50% - 70%), and hyperprolactinemia. Hypopituitarism is due to the absence or destruction of the pituitary[9]. Up to 32% of women experiencing hemorrhage and vascular collapse during delivery will develop some degree of hypopituitarism. The extent of pituitary necrosis and subsequent hypopituitarism are related to the severity of the hemorrhage[10]. The most important clue that pituitary necrosis has occurred is inability to lactate in the postpartum period and failure of cyclic menstruation restitution. Today, the most common cause of hypopituitarism is pituitary tumor[11].

Secondary hypopituitarism is due to the lack of stimulation of pituitary hormone secretion caused by organic or functional disorders of the vascular and/or neural connections with the brain at the level of the pituitary stalk, hypothalamus, or extrahypothalamic CNS.

Pituitary adenomas are the most common tumors affecting the hypothalamus, accounting for more than 90% of all pituitary neoplasms. Hyperprolactinemia occurs in about half of these tumors, caused primarily by disinhibition by the hypothalamus, with decreased dopamine reaching the pituitary[12,13].

Suprasellar dysgerminomas are said to arise from primitive germ cells that have migrated to the CNS during fetal life and are structurally identical to germ cell tumors of gonads. They usually present in children, in whom they most commonly cause growth retardation due to hypopituitarism, then diabetes insipidus, visual problems, and hyperprolactinemia (over 50%). Some 10% of patients have precocious puberty caused by the production of human chorionic gonadotropin (HCG) by the tumor.

Head trauma can cause defects ranging from isolated adrenocorticotropic hormone (ACTH) deficiency to panhypopituitarism with diabetes insipidus. Within the first 72 hours of trauma, blood levels of growth hormone (GH), luteinizing hormone (LH), ACTH, thyroid-stimulating hormone (TSH) and prolactin (PRL) may be elevated (perhaps as the result of an acute release). During prolonged observation, these levels fall and patients either return to normal or develop hypopituitarism, except for persistent PRL elevation in many cases[14]. These patients may or may not have associated loss of consciousness, but other neurologic abnormalities are common. In patients dying from head injury, anterior pituitary infarction was found in 16%, posterior pituitary hemorrhage in 34%, and hypothalamic hemorrhage or infarction in 42% of cases[15].

Whole brain irradiation for intracranial neoplasms results in hypothalamic dysfunction in 1.25% of patients, as evidenced by endocrine abnormalities and behavioral changes. The most common endocrine abnormality is hyperprolactinemia, however, when radiotherapy is targeted to the hypothalamic area or to the pituitary, a higher 10-year rate of clinically significant hypopituitarism has been recorded[16].

Hyperprolactinemia is the second major hypothalamic cause of amenorrhea and anovulation and female infertility, accounting for about 20% of cases. Hyperprolactinemia can also cause a decrease in GnRH secretion and cessation of pulsatile secretion[17]. When it occurs before puberty, it can prevent the onset of puberty and should always be looked for in this setting. Prolactin is the only hormone whose secretion is mainly under hypothalamic inhibitory control mediated by the release of dopamine into the portal pituitary circulation. Disruption of this system by a hypothalamic tumor, infiltrative disease (e.g., sarcoidosis), or surgical or traumatic stalk section can affect hypothalamic function, causing modest hyperprolactinemia.

Pituitary prolactinoma accounts for 50% of cases of hyperprolactinemia[18,19]. These tumors are classified into microadenomas (less than 1 cm in diameter) and macroadenomas (less common in women; they may extend suprasellarly, parasellarly or anterioinferiorly into the sphenoid sinus). The symptoms are oligo- or amenorrhea, galactorrhea, mild obesity, hirsutism, frictional dyspareunia, and loss of libido. The fairly good correlation between the level of prolactin and size of adenoma considerably helps in reaching the diagnosis, as serum levels greater than 200 ng/ml are almost always associated with prolactinoma, frequently macroadenoma[20].

Phenotiazines and other psychotropic agents antagonizing hypothalamic dopaminergic pathways are associated with mild to moderate elevations of prolactin concentration (up to four times normal). Amenorrhea occurs in 22% of female psychiatric patients with drug induced galactorrhea. Other medications associated with

hyperprolactinemia are metoclopramide, H2 histamine antagonists, calcium channel blockers, alfa methyldopa, and oral contraceptives. The symptoms generally resolve with medication discontinuation[21].

Idiopathic hyperprolactinemia is defined as hyperprolactinemia that occurs in the absence of any recognized pituitary, hypothalamic or other cause, and may manifest with amenorrhea, galactorrhea, impotence, infertility, and loss of libido.

Cushing's syndrome results from prolonged exposure of the body to high levels of glucocorticoid hormones. The cause can be exogenous, resulting from the administration of glucocorticoids or corticotropin (ACTH), or endogenous, secondary to increased secretion of cortisol or ACTH. It is most commonly iatrogenic, caused by glucocorticoid therapy[22]. Cortisol regulation involves feedback loops on the pituitary gland and hypothalamus. Spontaneous (endogenous) Cushing's syndrome can result from ACTH excess (ACTH dependent), which can arise from the pituitary gland or ectopic ACTH-secreting tumors, or from autonomous secretion of cortisol (ACTH independent) by a cortisol-secreting adrenal tumor or 'micronodular' adrenal glands. Amenorrhea is in part a consequence of androgen suppression of gonadotropin secretion. Approximately 70% of these cases of hypercortisolism are secondary to ACTH hypersecretion from the pituitary gland, a condition called Cushing's disease[23].

Pituitary adenomas are present in a vast majority of patients[1]. Hypersecretion of cortisol from the adrenal glands accounts for approximately 10% - 20% of cases of Cushing's syndrome. The underlying cause is adrenal adenoma in 50% - 60%, and adrenocortical carcinoma in 20% - 25% of cases. Bilateral adrenal hyperplasia accounts for the remaining 20% - 30% of cases.

Ectopic secretion of ACTH, referred to as ectopic ACTH syndrome, causes about 15% of cases of Cushing's syndrome[24,25]. In case of ectopic ACTH syndrome caused by ACTH hypersecretion from nonpituitary tumors, these tumors contain immunoreactive and bioactive ACTH, and they also secrete ACTH *in vitro*[26]. The tumors most commonly causing ectopic ACTH syndrome are oat cell carcinoma of the lung, pancreatic islet cell carcinoma, carcinoid tumors (lung, gut, thymus, pancreas, ovary), thyroid medullary carcinoma, pheochromocytoma, and related tumors[27].

Glucocorticoid-producing adrenal tumors arise *de novo* and autonomously hypersecrete cortisol and suppress the hypothalamic-pituitary axis, corticotropin-releasing hormone (CRH) and circulating plasma ACTH levels. Adrenal adenomas causing Cushing's syndrome usually secrete only cortisol in significant excess[28].

The onset of clinical progression of an ACTH-secreting pituitary adenoma after bilateral adrenalectomy for Cushing's disease is called Nelson's syndrome[29]. After adrenalectomy, the suppressive effect of cortisol is no longer present, ACTH secretion increases, and the adenoma may progress. The incidence of Nelson's syndrome ranges from 5% to 78%. About 30% of patients adrenalectomized for Cushing's syndrome have been found to develop classic Nelson's syndrome. Another 50% develop evidence of a microadenoma without marked progression, and about 20% never develop progressive pituitary tumor. The tumors in patients with classic Nelson's syndrome are among the most aggressive and rapidly growing of all pituitary tumors. These patients present with hyperpigmentation and manifestations of an expanding intrasellar mass lesion, usually within months to 2 years from adrenalectomy. Sellar enlargement, extrasellar extension, headache, visual field defects, and hypopituitarism are common. Invasion of the cavernous sinus or cranial fossae may lead to extraocular muscle palsies and other neurologic defects. These tumors can occasionally be frankly malignant with local invasion and extracranial metastases, and there is a high incidence of pituitary apoplexy (spontaneous hemorrhagic infarction of the tumor)[30].

The major ovarian causes of amenorrhea are hyperandrogenism, from internal to external sources, and ovarian failure due to normal or early menopause[31-33]. Premature ovarian failure can be defined as a syndrome of amenorrhea, hypoestrogenism, and elevated serum gonadotropin concentrations occurring before age 40. Ovarian failure occurs when the supply of oocytes and surrounding follicles is depleted. The lack of ovarian function leads to absolute estrogen deficiency, endometrial atrophy, and absence of menstruation[34]. This state can be idiopathic, associated with autoimmune ovarian destruction or karyotypic abnormalities, or induced by radiation or chemotherapy[35]. It is estimated that an autoimmune disease is present in approximately 30% of these patients, and associated with other autoimmune diseases, especially Hashimoto's thyroiditis and Addison's disease. Physical agents such as pelvic surgery, viral (mumps), oophoritis, gonadal irradiation, chemotherapy (cyclophosphamide or busulfan), and cigarette smoking are also known to cause transient premature ovarian failure[36].

The clinical and hormonal features are similar to those of the normal menopause and commonly develop over a

period of several years. Half of the patients present with clinical features of hypoestrogenism (mainly vaginal dryness and hot flushes), while secondary sexual characteristics are usually normal. If the condition develops around the time of menarche, the secondary sexual characteristics may be underdeveloped. As after the normal menopause, serum gonadotropin concentrations are elevated and hyperresponsive to GnRH, serum FSH levels may fluctuate in and out of the normal range, and serum estradiol levels may rise to the midfollicular range[37]. Neither clinical features nor the degree of FSH concentration elevation predicted which subjects would resume ovarian function. Little is known about the natural history of premature ovarian failure, although spontaneous resumption of menses and fertility may occur in some women. Genetic chromosomal abnormalities, particularly variants of gonadal dysgenesis, may present with premature ovarian failure. However, the majority of subjects have normal 46,XX karyotype. A family history of premature ovarian failure is found in 10% of subjects. Reports of vertical transmission of the trait are consistent with autosomal dominant or sex-linked inheritance.

Occult ovarian failure is a new syndrome of the clinical triad. Autoantibodies to adrenal or thyroid glands are present in 50%, and antiovarian antibodies in 40% of patients. A syndrome of 'incipient ovarian failure' has also been described, where inhibin levels are below the normal range and FSH is more markedly elevated than in occult ovarian failure[38].

In anorexia nervosa, amenorrhea occurs with reduction of body weight and fat. In severe cases, body weight may be as low as 25 kg. Treatment occasionally involves hospitalization for severe cachexia but primarily includes intensive psychotherapy. Rates of successful treatment vary but are improved by early diagnosis. Mortality rates of 0% to 19% have been reported.

Polycystic ovary syndrome is caused by inappropriately enhanced estrogen feedback or disturbance in the normal dopaminergic control of GnRH. There is a strong familial component to polycystic ovary syndrome. The syndrome includes oligo- or amenorrhea, infertility, hirsutism, obesity, and enlarged polycystic ovaries. Diagnosis is based on typical clinical features associated with an elevated LH/FSH ratio and increased plasma androgen levels. On ultrasonography, polycystic ovary syndrome is common in asymptomatic first-degree relatives of patients presenting with the syndrome. Irregular cycles in polycystic ovary syndrome can be controlled by a combination of an oral contraceptive and progestogen. Therefore, this common condition has heterogeneous clinical, anatomical and biochemical features.

Nutritional amenorrhea is caused by weight loss below 10% - 15% of ideal body weight. Many women of reproductive age are engaged in some kind of exercise, and most benefit from it in terms of improved exercise capacity, body weight control, and reduction of cardiovascular risk factors. However, excessive exercise at a critical time during development may delay puberty and menarche. Exercise alone does not induce amenorrhea. It appears that amenorrhea only occurs when there is relative caloric deficiency due to inadequate nutritional intake for the amount of energy expended. The hormone leptin is secreted by fat cells in proportion to body fat stores. Exercising women with amenorrhea lose the normal diurnal rhythm of leptin, raising the possibility that the diurnal rhythm is important for the maintenance of adult human reproductive function. Weight loss, particularly reduction in the percentage of body weight as fat, may occur if exercise programs are too difficult or dietary intake is inadequate (athletes, students matched for career stress). Resumption of menstruation and fertility usually accompanies the weight regain. If weight gain is not practicable, consideration should be given to replacement therapy to avoid the long-term sequels of hypoestrogenism.

Primary hypothyroidism, renal failure and liver cirrhosis as systemic diseases, and some local factors such as repetitive nipple stimulation, irriatative chest wall diseases (thoracic scarring or herpes zoster) also are reasons that lead to amenorrhea.

Diagnosis

Diagnostic procedures and studies must address two questions:

1) is pituitary hormone secretion diminished?, and

2) is the disorder of pituitary or nonpituitary origin?

Different etiologies have different clinical presentations. Difficulties in clinical diagnosis and especially in therapy are discussed below.

- Differential diagnosis
- Laboratory

If pregnancy test is negative, the following parameters should be determined: serum prolactin, FSH, LH, TSH, and blood sugar

- Pathologic findings
- Special tests: progesterone challenge test
- Imaging: ultrasonography, radiologic evaluation (CT, MRI)

– Diagnostic procedures: laparoscopy, hysterosalpingography

Diagnostic approach to amenorrhea implies diagnosis by exclusion. Pregnancy test is recommended as the first step in evaluating any woman with amenorrhea. Physical examination as the next step should begin with evaluation of pubertal development and careful genital examination.

Progesterone challenge test consists of oral administration of 10 mg medroxyprogesterone for 5 days. If withdrawal bleeding occurs, the amenorrhea is most likely due to anovulation. If there is no bleeding, estrogen status should be assessed. Once pregnancy and anatomical abnormalities have been excluded, all of the remaining causes of amenorrhea are associated with anovulation due to hypothalamic, pituitary, or ovarian disease. Determining the site of defect is clinically important because it determines the appropriate therapeutic regimen.

Whenever hypothalamic lesions are suspected, detailed evaluation of the hypothalamic-pituitary function is indicated. The workup for Cushing's syndrome should be aimed first at establishing the diagnosis. The state of hypercortisolism must be documented. Adult adrenal glands secrete 10-30 mg cortisol daily on an average. The secretion follows diurnal variation: cortisol levels tend to be high early in the morning and low in the evening. To determine the etiology of an elevated cortisol level, plasma ACTH levels must be checked. ACTH secretion is evaluated by the measurement of plasma ACTH and cortisol levels. Cortisol measurement is a more useful screening procedure: morning values of <10 mg/dl or <20 mg/dl under stress conditions are suggestive of hypopituitarism. In contrast to patients with primary adrenal insufficiency, those with hypopituitarism may exhibit no appreciable clinical symptoms and yet have nearly undetectable circulating cortisol levels. A low or even normal ACTH level in the presence of low cortisol level is highly indicative of a primary adrenal disease. If cortisol levels are normal and an intact response to ACTH is present, the hypothalamic-pituitary axis should be evaluated[39].

Hyperprolactinemia can decrease GnRH and pulsatile secretion of LH and FSH[40]. As gonadotropin responses to GnRH are normal in hyperprolactinemia, it appears that elevated prolactin levels act at the hypothalamic level. Hyperprolactinemia also inhibits positive estrogen feedback. If the hyperprolactinemia is caused by pituitary prolactinoma (50% of all hyperprolactinemia cases), the hormones show sustained hyperprolactinemia (often of a marked degree), normal or suppressed serum gonadotropin levels, and estrogen production. Prolactin elevation caused by hypothalamic lesions rarely rise to greater than 150 ng/ml and usually are below 100 ng/dl. Similar elevations are also seen in patients with an empty sella. The prolactin level correlates with pituitary tumor size. It is interesting that prolactin levels can be increased in patients with hypothalamic lesions while other hypothalamic-pituitary functions (i.e. ACTH and TSH) are normal, although GH levels and gonadotropin levels are also often suppressed. This means that there is enough destruction or distortion of the stalk and/or mediobasal hypothalamus to cause deficiency of dopamine while permitting sufficient CRH and TRH secretion. Idiopathic hyperprolactinemia usually shows prolactin levels below 100 ng/ml[41,42].

In case of premature ovarian failure, weekly serum gonadotropin determinations and tests of urinary estrogen and progesterone excretion over a 6-week period will provide a true baseline estimate of any ovarian follicular activity. Karyotyping is performed in nulliparous patients. Ovarian biopsy has been emphasized by some authors as necessary to differentiate oocyte depletion from gonadotropin-resistant ovary syndrome, which is allegedly amenable to treatment[43].

The diagnosis of polycystic ovary syndrome is based on typical clinical features associated with an elevated plasma LH/FSH ratio and increased plasma estrogen levels. On ultrasonogrpahy, the syndrome is commonly found in asymptomatic first-degree relatives of patients with the disease.

Yearly bone mineral density measurement is a crucial method that should be recommended for early detection in all women of menopausal age.

However, dynamic testing of pituitary function will often fail to differentiate between the hypothalamus and pituitary as the specific primary locus of defect, and neuroradiologic imaging by MRI or CT is almost always required. The main indications for MRI or CT scanning include primary hypogonadotropic hypogonadism, visual field defects, headaches, other evidence of hypothalamic or pituitary dysfunction, or other suggestive diseases. In case of tumor (adenoma, prolactinoma, cysts) or lesion (head trauma) induced amenorrhea, the essential examination is high resolution CT and MRI scanning. CT may be better in detecting small lesions within the normal or minimally enlarged gland. MRI is superior in visualizing structures adjacent to the pituitary, which is often the most significant issue. Abdominal CT scan will help separate an adrenal neoplasm from primary adrenal hyperplasia.

Therapy

Resumption of menstruation and fertility depends on the etiology of amenorrhea. Conservative therapy is the first choice. In patients with idiopathic, functional hypogonadotropic amenorrhea, there are two goals: facilitating ovulation to achieve fertility, and restoration of normal estrogen status to promote well-being and to prevent osteoporosis. The former can generally be achieved with cyclic estrogen and progesterone, whereas the latter may require clomiphene, GnRH, or gonadotropin therapy.

The ideal for patients with GnRH deficiency is GnRH replacement therapy. Subcutaneous administration of 25 to 200 ng/kg GnRH every 2 hours by a portable pump leads to rapid rise in LH and FSH responses to GnRH. Such therapy has led to ovulatory cycles in 80% of patients, confirming the original hypothesis of a primary defect of GnRH secretion. An adequate level of sex steroids is necessary for normal GH response in case of growth hormone deficiency associated amenorrhea, and sex hormone replacement is not used in these patients before GH testing.

Therapy for osteoporosis includes exercise and drugs. The drugs used to treat osteoporosis are classified into antiresorptive and formation-stimulating agents. Antiresorptive agents such as calcium, estrogen, calcitonin, vitamin D and biphosphonates, are used mainly for prevention in perimenopausal women or for treatment of established osteoporosis. Fluoride is the only formation-stimulating agent. Currently, the only therapy that prevents the accelerated bone loss associated with menopause and other causes of ovarian failure is estrogen replacement. This therapy should be initiated within 4 to 6 years of menopause to achieve its maximal effect. After that, irreversible bone loss will have occurred.

In the management of hyperprolactinemia, bromocriptine, a dopamine agonist, has been established as the drug of choice. The hyperprolactinemia itself may impair gonadal function and so efforts may also be made to lower prolactin levels with bromocriptine or another dopamine agonist. Periodic monitoring of basal prolacin levels and radiographic evaluation of sella turcica are indicated in all subjects with hyperprolactinemia. Patients should be evaluated at least quarterly and should undergo repeat CT or MRI annually for at least additional 2 years. Control of hyperprolactinemia using bromocriptine is followed by restoration of ovulatory menses and fertility, and abolition of galactorrhea in 78% - 85% of all patients, and in more than 90% of those with idiopathic hyperprolactinemia. A dramatic reduction in tumor volume is seen in up to three quarters of patients.

The regain of weight and cessation of exercise are the best therapy for exercise and anorexia nervosa related amenorrhea. If weight gain is not practicable, consideration should be given to estrogen replacement therapy to avoid long-term sequels of hypoestrogenism. Treatment may occasionally involve hospitalization for severe cachexia, however, it primarily includes intensive psychotherapy. The use of combined oral contraceptive and progestogen can control irregular cycles of polycystic ovary syndrome.

Treatment components

- appropriate health care: patient education, proper food intake, exercise
- drugs
- surgical procedures

Therapy for premature ovarian failure involves replacement of cyclic estrogen and progesterone for the maintenance of normal secondary sex characteristics and libido, and avoidance of long-term sequels of hypoestrogenism. High-dose exogenous gonadotropin therapy has occasionally been associated with pregnancy, but the results are generally disappointing. The majority of patients with premature ovarian failure who subsequently conceive have been exposed to estrogen. None of these therapies for premature ovarian failure has been subjected to proper prospective trial with due regard to the variable natural history of premature ovarian failure and spontaneous pregnancy rate.

Operative management of tumor (adenoma or prolactinoma) is limited to subjects who are intolerant of or resistant to conservative therapy (bromocriptine), and those with tumors causing compressive symptoms, where bromocriptine has had an inadequate effect. Evidence that hypopituitarism results from pituitary compression includes a low serum prolactin level and lack of TSH response to TRH. In such cases, pituitary function usually does not improve with treatment. In patients with normal or elevated prolactin levels, pituitary function often returns to normal with therapy[17].

Selective removal of pituitary microadenomas by transsphenoidal microsurgery corrects ACTH hypersecretion and hypercortisolism in most patients. Surgical extirpation of the tumor commonly leads to worsening of pituitary function, often resulting in complete panhypopituitarism and diabetes insipidus because of stalk sec-

tion[46,47]. Radiotherapy is palliative therapy, and dysgerminomas are the only tumors that are very radiosensitive, thus radiotherapy being the preferred mode of treatment[47].

Follow-up

- patient monitoring: depends on the cause and treatment chosen
- prevention/avoidance: maintenance of proper body mass index
- possible complications: estrogen deficiency symptoms, osteoporosis, increased risk of endometrial cancer in hyperestrogenism
- expected course/prognosis: reflecting the underlying cause

Conclusions

Appropriate management of amenorrhea depends on the underlying etiology. As described above, a number of different pathologic processes can cause amenorrhea. Even physiologic amenorrhea in third age of women's life can lead to serious health problems. Many symptoms in climacteric women can be more important than the simple clinical picture. Psychiatric problems (chronic depression), cardiovascular disease, and osteoporosis are some of the greatest problems, often encountered at general practitioner offices. However, the problems faced by women with amenorrhea are much deeper. Very important is the time when substitution for estrogen deficit is initiated. A high proportion of women with amenorrhea first experience the symptoms of vaginal dryness and skin pruritus associated with low estrogen levels. Estrogen substitution is also helpful in postmenopausal women suffering from hot flushes. Combined therapy with estrogen and progesterone can protect women from severe malignancies (endometrial carcinoma).

Untreated pituitary tumor (Cushing's disease, prolactinoma and nonfunctional tumors) frequently is a fatal illness. In many cases, death is the consequence of sustained hypercortisolism and hyperprolactinemia and its complications, including hypertension, cardiovascular disease, stroke, thromboembolism, and susceptibility to infection. With current refinements in pituitary microsurgery and radiotherapy, the great majority of patients with Cushing's disease can be successfully treated, and operative morbidity and mortality are no longer present. The rates of successful treatment vary but are improved by early diagnosis. Therefore, this condition has heterogeneous clinical, anatomical and biochemical features that result in clinical difficulties hampering both diagnosis and therapy.

The menstrual cycle is relatively susceptible to external influences, and changes in menses may be the earliest sign of a decline or improvement in general health. Some untreated cases may even have lethal outcome.

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Sažetak

S KAKVIM JE ZDRAVSTVENIM RIZIKOM UDRUŽENA AMENOREJA?

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Amenoreja je jedan od najčešćih simptoma u ženskoj patologiji. Ona može biti uzrokovana anatomskim nedostacima izlaznoga trakta (maternica, ušće maternice, rodnica) pa spada u djelokrug ginekologa, no može se zapaziti kod bolesti nedostatka gonada (npr. Turnerov sindrom), hipopituitarizma (npr. Sheehanov sindrom), u bolesnika s tumorima hipofize koji luče prolaktin, kod Cushingova sindroma, hipertiroze, stresa, anoreksije nervosa, policističnih jajnika, te nakon prestanka uzimanja oralnih kontraceptiva, poglavito u žena s prethodnim menstrualnim nepravilnostima u anamnezi. Endokrine abnormalnosti mogu isto tako biti uzrokovane promjenama u odgovoru ciljnih tkiva na hormone. Različiti mehanizmi mogu biti uključeni u nastanak ovih bolesti. Endokrine žlijezde mogu biti oštećene ili uništene neoplazijom, infekcijama, krvarenjem, autoimunim bolestima, te mnogim drugim uzrocima. Najčešći uzroci amenoreje su menopauza, trudnoća i dojenje. Oštećenja hipotalamusa koja dovode do poremećenog lučenja hormona za otpuštanje mogu se očitovati disfunkcijom hipofize, što opet rezultira funkcionalnim abnormalnostima različitih ciljnih organa. Poremećaji izvan te žlijezde mogu dovesti do pomanjkanja hormona i postati očitima, uz amenoreju kao jedan od simptoma. Procjena endokrinog statusa bolesnice temelji se na nalazima iz anamneze, fizikalnog pregleda i laboratorijskih pretraga. Laboratorijski testovi mogu uključivati mjerenje razina hormona ili njihovih metabolita u plazmi ili mokraći u bazalnom stanju ili u odgovoru na provokativno testiranje. Kod sindroma endokrine deficijencije hormoni se uglavnom daju kako bi se ispravila ta deficijencija. Kod sindroma s viškom hormona primjenjuju se različiti pristupi. Tumori koji pokazuju hiperfunkciju se odstranjuju kadgod je to moguće, a ponekad se uklanjanju i hiperplastične žlijezde. U drugim pak slučajevima daju se lijekovi za suzbijanje stvaranja hormona. Osteoporoza povezana s menopauzom vodeći je zdravstveni problem povezan s amenorejom i treba ju što ranije liječiti, tj. od početka razdoblja prestanka menstruacije.

Ključne riječi: *Amenoreja, etiologija; Amenoreja, dijagnostika; Amenoreja, komplikacije; Osteoporoza, etiologija; Osteoporoza, prevencija i kontrola*