Menstrual Disorders Related to Endocrine Diseases

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Contents

Abstract

Endocrine disturbances affecting the menstrual cycle and fertility in women can interfere with the coordinated stimulatory and inhibitory effects that lead to the release of a single mature oocyte from the ovarian pool of primordial oocytes. The female reproductive system may be susceptible to dysfunction generated by internal and external forces that include disorders in alimentation, excess exercise, psychophysical stress, and pathologies. This report examines the influence of neuroendocrine and pituitary dysfunctions and adrenal, thyroid, local, and systemic pathologies on the female reproductive axis. These disorders can modify a variety of factors that contribute to abnormal uterine bleeding, and they include steroidal and nonsteroidal hormones and paracrine, autocrine, and intracrine factors. All these substances can alter the cyclic changes in the major pituitary and gonadal hormones and the related feedback mechanism involved in the normal menstrual cycle. Pathologies of the hypothalamus can cause pituitary dysfunction, neuropsychiatric and behavioral disorders, and resulting menstrual disorders. The anterior

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pituitary gland controls the secretion of essential hormones from other endocrine glands including gonads, thyroid, and the adrenal cortex, and its disorders – partial or complete – can greatly influence the normal menstrual cycle. The ovarian sex steroids and their cognate receptors regulate an array of local factors within the endometrium that lead to important paracrine, autocrine, and intracrine actions in the regulation of menstruation. Endometrial intracrinology, associated with altered expression of key enzymes within the cells, has recently opened up new routes in understanding the development of menstrual disorders mediated by endocrine diseases.

Keywords
Female reproductive axis · Menstrual disorders · Ovary · Hypothalamus · Pituitary · Adrenal · Thyroid · PCOS · Gonads · Neuroendocrine system · LH · FSH · Estradiol · Gonadotropins

Introduction

The normal menstrual cycle is a coordinated series of systemic and local effects that results in ovulation and the decidualization of endometrial stromal cells to prepare for embryo implantation. By tradition, the cycle is divided into two periods: the proliferative follicular phase, which begins with the onset of menses and ends on the day before the LH surge, and the secretive luteal phase, which starts on the day of the LH surge and ends on the first day of menstruation, for an average of 28–35 days (Barbieri 2014). The gonadotropins secreted by the anterior pituitary control the ovarian activity through feedback mechanisms mediated by estradiol and progesterone. Evidence has been provided that even nonsteroidal substances, such as inhibin A and B, and the recently described gonadotropin surge-attenuating factor (GnSAF), participate in the negative feedback (Messinis et al. 2014), playing a role in the control of LH secretion during the follicular phase and at midcycle (Jabbour et al. 2006).

Over the last decade, genetic and genomic research has added information about the neuroendocrine control of the menstrual cycle (Genazzani et al. 1997; Leng and MacGregor 2018). The hypothalamic gonadotropin-releasing hormone (GnRH), the main neuropeptide controlling the reproductive axis, is regulated upstream in its pulsatile activity mainly by neurokinin B, kisspeptin, and the inhibiting makorin ring finger protein 3 (MKRN3), which negatively controls the release of GnRH from the hypothalamus, modulating the onset of puberty (Tsutsui and Ubuka 2018; Livadas and Chrousos 2016). Thus, abnormal uterine bleeding may arise from the imbalance of many clinical pathologies and cause significant reproductive disorders. Many endocrine disorders can affect the complex network of neuroendocrine and pituitary function, modifying ovarian steroid hormone production which regulates endometrial function and human menstruation.

Once ovulation has occurred, the corpus luteum secretes progesterone. In the mid-luteal phase, the action of progesterone upon the estrogen-primed endometrium

promotes decidualization, converting the elongated endometrial stromal cells into more spherical decidual cells. This induces the expression of two hemostatic proteins in decidualized endometrial stromal cells: the tissue factor (TF), a 46 kDa cell membrane-bound glycoprotein that acts as a receptor for the active form of coagulation factor VII, and the plasminogen activator inhibitor-1 (PAI-1) that controls trophoblast invasion and cooperates in maintaining anti-fibrinolytic and anti-proteolytic properties together with angiopoietin-1, an angiostatic agent that stabilizes the vessels blocking uncontrolled angiogenesis. Simultaneously with the corpus luteum regression, there is a reduction in TF, PAI-1, and angiotensin-1, and the endometrium becomes infiltrated by leukocytes, cytokines, and matrix metalloproteinases (Gellersen and Brosens 2014).

Therefore, during the late secretory phase of the menstrual cycle, progesterone withdrawal creates a pro-hemorrhagic environment around the endometrial blood vessels, provoking endometrial inflammation and local cytokine presence and the initiation of menstruation. Matrix metalloproteinases (MMPs) are considered the main mediators of endometrial breakdown, considering that they have the ability to degrade all components of the extra cellular matrix (ECM). In addition to chemokine release, an important point is the endometrial vascular effects activated by progesterone withdrawal and the intense vasoconstriction observed which induces endometrial shrinkage. Progesterone withdrawal is associated with upregulation of interleukin-8 and macrophage chemoattractant protein-1. Hypoxia may occur at menstruation in human endometrial tissue, and, even if its function must be still fully clarified, it has been demonstrated that it enhances angiogenesis by inducing endometrial stromal cells to express the vascular endothelial growth factor (VEGF) and endometrial endothelial cells to express angiopoietin-2 participating in the MMP release and tissue destruction (Maybin and Critchley 2015).

A higher expression of TNFα, a pro-inflammatory cytokine, has been described in the flaked endometrium of women affected by menstrual disorders compared with women with a normal menstrual period (Malik et al. 2006). Glucocorticoids may alter the inflammatory response by limiting the cytokine production, increasing both macrophage phagocytosis and the transcription of anti-inflammatory transcription factors that repress the pro-inflammatory machinery. The glucocorticoid receptor is expressed on stroma cells, endometrial leukocytes, and endothelial cells, and the local availability of glucocorticoids may be important in endometrial physiology.

To summarize, during the luteal and gestational phase, the action of factors inducing stabilization of the stromal and underlying vascular extracellular matrices prevents endometrial shrinkage and cleavage. In contrary fashion, perimenstrual progesterone withdrawal in the absence of fertilization is associated with increased expression of prostaglandins and chemokine release, promoting leukocyte infiltration, vascular effects inducing hypoxia and increased expression of VEGF, and MMP activation and release in a general proteolytic milieu that causes tissue destruction (Malik et al. 2006).

Beyond the effects of endocrine dysregulation, menstrual disorders can be generated by a disruption of the well-ordered and highly regulated autocrine-paracrine/intracrine processes underlying endometrial physiology, inducing excessive tissue

damage and/or prolonged inflammatory response at the time of menstruation. In this area, menstrual disorders may be related to lifestyle and physical and emotional stress and traumas. Menstrual dysfunction includes menorrhagia; dysmenorrhea; irregular, frequent, and prolonged periods; oligomenorrhea; amenorrhea; and abnormal uterine bleeding (AUB) caused by both local and systemic pathologies or related to medication (Lockwood 2011).

The most common etiologies encompass uterine pathologies (like adenomyosis, leiomyomas, polyps, endometrial hyperplasia, endometriosis, endometrial cancer, or, albeit rarely, intrauterine adhesions or synechiae). Many of these disorders are associated with a dysfunction of the hypothalamic-pituitary-ovarian axis, and they induce morphological changes within the uterus that are not related to modifications in the activity of endometrial local factors. Menstrual disorders can originate from primary or secondary ovarian failure, the dysregulation of gonadotropin secretion, and polycystic ovary syndrome (PCOS) (Gray 2013). The aim of this chapter is to focus mainly on neuroendocrine and pituitary dysfunctions and adrenal and thyroid pathologies that can induce menstrual disorders.

Menstrual Disorders and Hypothalamic Pathologies

After the gonadotropin-releasing hormone (GnRH) – the regulator of the production and release of the pituitary gonadotropins – was isolated and characterized, the central role of this decapeptide in the reproductive function was established. GnRH is synthesized in a small subset of hypothalamic neurons which differentiate in the olfactory placode and migrate to the medial basal hypothalamus where they establish a close morphofunctional connection with the pituitary portal system in the median eminence as part of the hypothalamic portal system. The discovery of a gonadotropin-inhibitory hormone (GnIH), highly conserved among vertebrates, that acts by inhibiting gonadotropin synthesis and release by acting on gonadotropes and GnRH neurons (Tsutsui et al. 2018) indicates that GnRH is not the only hypothalamic neuropeptide able to regulate gonadotropin release. GnRH in the anterior pituitary gland binds to specific receptors (GnRHRs) expressed on gonadotroph cells, triggering an intracellular signaling cascade that involves the α_q-subunit of G-protein which activates phospholipase Cβ leading to an intracytoplasmatic increase in diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3), and therefore, through the activated protein kinase C (PKC), to the release of Ca^{2+} from intracellular stores (Maggi et al. 2016). To be activated, pituitary GnRHRs require a pulsatile stimulation by GnRH. In fact, the presence both in females and in males of a physiological reproductive function that is dependent on the pulsatile pattern of GnRH secretion and many neuromodulators has been identified as being involved in this mechanism (Stamadiates and Kaiser 2018). The distribution and episodic activity of GnRH-producing neurons and the network of neurotransmitters and neuropeptidergic inputs, modulating its pulsatile secretion, drive many events connected to the onset of the menstrual cycle and to the regulation of the physiological ovarian function (Maggi et al. 2016). Developmental defects of GnRH

neuron migration or the inability of the hypothalamus to release GnRH in the correct pulsatile manner can lead to a wide range of disorders, identified overall as central hypogonadotropic hypogonadism (Fourman and Fazeli 2015).

Genetic studies to date have identified at least 16 genes affecting the development and function of the GnRH neurons, and in patients with isolated GnRH deficiency, they have highlighted either forms with olfactory dysfunctions (Forni and Wray 2015), referred to as Kallmann syndrome, or forms occurring with a normal sense of smell (Valdes-Socin et al. 2014). Female patients with isolated GnRH deficiency rarely develop clinical features at birth, but they have them at the onset of puberty (amenorrhea and a failure to establish a pubertal growth spurt), demonstrating inappropriately low or high (but also normal) luteinizing hormone (LH) and follicle-stimulating (FSH) that may arise when administered in a pulsatile regimen designed to mimic GnRH secretion. This demonstrates the intact anatomic and functional integrity of pituitary and gonads. In most cases of central hypogonadotropic hypogonadism, sporadic familial transmission has been described. This is because either anosmic or non-anosmic forms can be inherited in an autosomal dominant, autosomal recessive, or X-linked recessive manner. An oligogenic inheritance has been recognized as contributing to incomplete penetrance and variable expressivity that occurs within and across affected families (Marino et al. 2014). Table 1 shows genes that typically cause the anosmic and normosmic forms of central hypogonadotropic hypogonadism.

As mentioned above, a huge number of signals are involved in the control of GnRH neuron function and secretion. The mechanism underlying pulsatile secretion arises from a fine-tuned modulation addressed to induce a correct secretion of LH and FSH from pituitary gonadotrophs. Ovarian steroids through their nuclear receptors exert differential regulatory effects on GnRH secretion, altering both pulse frequency and amplitude. 17β-Estradiol may have both stimulatory and inhibitory effects, depending on the stage of the menstrual cycle. On the estrogen-primed endometrium, progesterone exerts an inhibitory action slowing the frequency of GnRH pulsatile secretion.

In addition to the modulatory action exerted by the ovarian steroids, a network of neurons afferent to GnRH neurons in the infundibular region and arcuate nucleus may control their pulsatile activity, whereas in humans the preoptic area mediates the surge phase. In this neural network, a relevant role is played by kisspeptin and neurokinin B neurons that are mainly present in the infundibular tract and in the preoptic area. Kisspeptin (KP) signals via a $G\alpha_{q/11}$/β-arrestin-coupled kiss1 receptor (KISS1R), whose expression on GnRH cell bodies is largely dependent on ovarian estradiol output, control the hypothalamic-pituitary-ovarian axis and are important in promoting endometrial gland development and function (Leon A). Neurokinin B is co-expressed in KP neurons (KNDy neurons) operating upstream of KP to modulate downstream GnRH pulsatility together with other peptides such as dynorphin and substance P (Skorupskaite et al. 2014). The hypothalamic neural network controlling GnRH pulse frequency and amplitude is also highly regulated by peripheral peptides from the adipose tissue and gastrointestinal tract, in particular leptin and ghrelin whose changes are related to the energy stores. Leptin and ghrelin are antagonists in

Table 1 Most significant genes implicated in hypogonadotropic hypogonadism

Gene	Location	Inheritance	Phenotype
KAL1	Xp22.3	X-linked	KS ± synkinesia and renal agenesis
FGFR1	8p11.23-p11.22	Autosomal dominant	KS, IHH ± clefting
FGF8	10q24.32	Autosomal dominant	KS, IHH
FGF17	8p21.3	Autosomal dominant or autosomal recessive with oligogenicity	KS, IHH
IL17RD	3p14.3	Autosomal dominant or autosomal recessive with oligogenicity	KS ± deafness
DUSP6	12q21.33	Autosomal dominant or autosomal recessive with oligogenicity	KS, IHH
SPRY4	5q31.3	Autosomal dominant or autosomal recessive with oligogenicity	KS, IHH
FLRT3	20p12.1	Autosomal dominant or autosomal recessive with oligogenicity	KS
HS6ST1	2q14.3	Autosomal dominant or autosomal recessive with oligogenicity	KS, IHH
NELF	9q34.3	Autosomal dominant or autosomal recessive with oligogenicity	KS
WDR11	10q26.12	Autosomal dominant	KS, IHH
PROKR2	20p12.3	Autosomal dominant or autosomal recessive with oligogenicity	KS, IHH
PROK2	3p13	Autosomal recessive	KS, IHH
CHD7	8q12.1-q12.2	Autosomal dominant	CHARGE, KS, IHH
SEMA3A	7q21.11	Autosomal dominant or autosomal recessive with oligogenicity	KS
SEMA3E	7q21.11	Autosomal dominant or autosomal recessive with oligogenicity	KS
SOX10	22q13.1	Autosomal dominant or autosomal recessive with oligogenicity	KS ± deafness
FEZF1	7q31.32	Autosomal recessive	KS
TAC3	12q13.3	Autosomal recessive	IHH
TAC3R	4q24	Autosomal recessive	IHH
KISS1	1q32.1	Autosomal recessive	IHH
KISS1R	19p13.3	Autosomal recessive	IHH
GnRH1	8p21.2	Autosomal recessive	IHH
GnRHR	4q13.2	Autosomal recessive	IHH

KS Kallman syndrome, *IHH* idiopathic hypogonadotropic hypogonadism

their effects on GnRH neurons, and changes in their function can occur linked to hypogonadotropic hypogonadism, precocious and delayed puberty, hypothalamic amenorrhea, perimenopausal transition phase, PCOS, and endometriosis (Celik et al. 2015).

Many menstrual disorders and much ovulatory dysfunction may be dependent on the dysregulation of the hypothalamic machinery that controls GnRH pulsatility (Coss 2018). Intense exercise, eating disorders, and stress can markedly affect the normal menstrual cycle. The female athlete triad is an interrelationship of menstrual dysfunction, low energy availability (with or without an eating disorder), and decreased bone mineral density (Nazem and Ackerman 2012). Energy availability, through different pathways, seems to be the key etiological factor in this condition, even if the impact of nutrient reduction (an often conscious restriction of food intake) on menstrual disorders can be modified in particular by gynecological age, psychological factors, and genetics (Williams 2017). Individuals with anorexia nervosa and amenorrhea have severe bone loss (Schorr and Miller 2017), and the restoration of a normal GnRH pulse frequency is possible only if the recovery of fat mass – determined using DXA – is over 20% of body weight (personal observation). Organic disorders of the hypothalamus can cause pituitary dysfunction, neuropsychiatric and behavioral disorders, and disturbances of autonomic and metabolic regulation. Craniopharyngiomas are rare and are partly cystic and calcified embryonic malformations of the sellar/parasellar region that have a peak incidence rate at the puberty time, altering its time of onset. However, they can arise in adults, in particular over the age of 50. Despite high survival rates, the quality of life of the patients affected is often impaired because of the sequelae caused by the anatomical proximity of the tumor to the optic nerve/chiasma and pituitary (Müller 2014). Other rare intracranial tumors (like meningiomas, ependymomas, gliomas) may affect the hypothalamic areas, causing neuroendocrine dysfunctions and menstrual cycle abnormalities (Table 2).

To summarize, neuroendocrine amenorrhea often primarily affects adolescent women because of perturbations of the hypothalamic function, most frequently in response to physical, emotional, or nutritional stress and rarely because of tumors or infectious diseases.

Menstrual Disorders and Pituitary Pathologies

The anterior pituitary gland controls the secretion of the major endocrine glands, and its activity is modulated by inputs from higher brain centers to the hypothalamus that produce releasing and inhibitory neurohormones, leading to a release of pituitary and target gland hormones. Target gland hormones in turn exert a feedback action at both hypothalamus and pituitary levels, influencing metabolism and diurnal rhythms. As far as the female reproductive axis is concerned, GnRH secreted by the hypothalamus regulates the synthesis and secretion of gonadotropins, LH, and FSH, which then control steroidogenesis and gametogenesis. In women, serum LH and FSH produced by the gonadotroph cells of anterior pituitary exhibit rhythmic changes throughout the menstrual cycle that are correlated with pulse frequency of GnRH (Coss 2018). Here, dysfunctions in the LH/FSH ratio due to levels outside the normal range may be caused by drugs or exogenous hormones or linked to several endocrine diseases, even affecting other axes controlled by the pituitary gland. One

Table 2 Most common neuroendocrine causes of menstrual dysfunctions

Overall
Stress-induced functional hypothalamic amenorrhea
Damage from pituitary radiation therapy
Traumatic brain injury
Tumors
Craniopharyngioma
Glioma, meningioma
Pituitary macroadenomas
Angioma, plasmacytoma, colloid cysts
Lymphoma
Ependymoma
Sarcoma
Histiocytosis X
Inflammatory disease
Tuberculosis
Viral encephalitis
Vascular diseases
Aneurysm, subarachnoid hemorrhage
Arteriovenous malformation

paradigmatic dysfunction of the brain-hypothalamic-pituitary axis is anorexia nervosa, a psychiatric disorder characterized by altered body image, persistent food restriction, and low body weight and fat mass. In this condition, a hypogonadotropic hypogonadism is evident with relative estrogen and androgen deficiency that induces secondary amenorrhea together with growth hormone resistance, hypercortisolemia, hyponatremia, hypooxytocinemia, hypoleptinemia, and elevated plasma levels of ghrelin and peptide YY – all endocrine disturbances secondary to the low energy state of chronic starvation (Schorr and Miller 2017).

The pituitary gland is made up of an anterior lobe of epithelial origin and a posterior lobe of neural origin. Pathologies of either the anterior or posterior lobe are associated with symptoms derived from the hyper- or hypo-secretion of the different cell types involved, the growth hormone (GH), prolactin (PRL), adrenocorticotropin (ACTH), and gonadotropin (FSH/LH) secreting cells. Nonfunctioning adenomas are not identified for the dysregulated specific hormone secretion but frequently for mass effects causing headache, hypopituitarism, and visual field defects. Most of these "nonfunctional" tumors derive from the glycoprotein hormone cell lineage and express mRNA for the common α-subunit of pituitary glycoprotein hormones (LH, FSH, TSH), giving rise to biologically inactive products (Melmed 2015). Almost all anterior pituitary adenomas are benign. Locally aggressive and invasive carcinomas are extremely rare, and they are often diagnosed when distant metastases are detected. The survival of subjects affected with pituitary carcinomas is usually less than 2 years after diagnosis (Raverot et al. 2018). Senescence, characterized by a signal transduction program leading to irreversible cell-cycle arrest, seems to

represent a key protective mechanism against malignancy, mostly mediated by the action of interleukin-6 (IL-6), restraining a proliferative advantage and allowing pituitary cells to maintain their physiological functions (Sapochnik et al. 2017). The pituitary adenomas most frequently involved in the pathogenesis of secondary amenorrhea are prolactinomas which account for more than 60% of all adenomas causing galactorrhea and infertility in women (Molitch 2017). The diagnosis of prolactinoma is difficult given that hyperprolactinemia has many potential etiologies. The stress of phlebotomy may induce a rise in serum prolactin, and false elevated levels can be due to macroprolactin, also known as "big prolactin," a non-bioactive prolactin isoform usually composed of a prolactin monomer and an IgG molecule having a prolonged clearance rate similar to that of immunoglobulins. This isoform is clinically non-reactive but it interferes with immunological assays used for the detection of prolactin (Vaishya et al. 2010). The clinical expression of cell-specific prolactinomas is associated with a loss of libido, oligomenorrhea, galactorrhea, and infertility.

The diagnosis is made even more difficult because a pituitary adenoma not secreting prolactin might induce hyperprolactinemia stalk compression and obstacles to dopamine delivery. Plasma levels of prolactin are related to the size of prolactinoma evaluated on T1-weighted MR, and the size of the tumor tends to shrink with therapy given that prolactinomas are very responsive to medical therapy with dopamine agonists (bromocriptine and cabergoline). Cabergoline used in early pregnancy was not found to increase the risk of miscarriage or fetal malformations. Surgery and radiotherapy are limited to rare tumors unresponsive to dopamine agonists. One growth hormone is prolactogen; therefore, amenorrhea-galactorrhea and mild hyperprolactinemia can be due to a somatotropinoma. Somatotroph adenomas are rare, accounting for around 12% of all pituitary tumors and leading to features of acromegaly with the enlargement of bone extremities, lips, tongue, and nose and symptoms of arthritis, hypertension, headache, and hyperglycemia. Symptoms are subtle and gradual in onset and thus diagnosis can be late. The assessment of IGF-1 plasma levels represents the best screening test for acromegaly, and GH suppression with 75 gr of anhydrous glucose is used as a confirmation test. Many somatotropinomas express somatostatin receptors, mainly the sub-type 2, and are responsive to somatostatin analogs such as octreotide or lanreotide, even if large tumors require both transsphenoidal surgery and medical therapy.

Thyrotroph adenomas hypersecreting TSH are extremely rare and may be associated with mild hyperthyroidism and goiter. Corticotroph adenomas are extremely rare and produce hypercortisolism associated with disorders of the menstrual cycle, infertility, central obesity, hypertension, diabetes, and psychological disorders. A pathogenetic feature of all these tumors is their monoclonality as they appear to arise from a single cell that causes an activating mutation of the specific receptors binding the hypothalamic hormones that acquire a proliferative advantage. Their surgical resection may result in long-term remission. While 95% of pituitary adenomas arise sporadically without a known inheritable predisposing mutation, in about 5% of cases, they can arise in a familial setting, either isolated (familial isolated pituitary adenoma or FIPA) or as part of a syndrome (Pepe et al. 2019).

Whatever the case, case abnormalities in cell-cycle regulation are seen as the key event in the pathogenesis of pituitary adenomas with multiple pathways involved, due either to germline mutations or to altered gene expression, inducing isolated pituitary adenomas or syndromic diseases (Caimari and Korbonits 2016). Among the syndromic diseases, the multiple endocrine neoplasia type 1 (MEN1) is characterized by the presence of the classic triad of hyperparathyroidism (in over 90% of patients by the age of 50 years), gastroenteropancreatic neuroendocrine tumors – NETs (in approximately 60% of patients), and pituitary adenomas (in about 35% of patients), besides the possibility of association with other endocrine and non-endocrine tumor types such as bronchial and thymic NETs, facial angiofibromas, lipomas, collagenomas, adenomas of the adrenal cortex, meningiomas, breast cancer, and, rarely, pheochromocytomas (Pepe et al. 2019). MEN1 is due to germline heterozygous mutations in the *MEN1* gene which encodes menin, a scaffold protein located mostly in the nucleus and involved in several cellular processes, including transcriptional regulation, genome stability, and cell division and proliferation (Pepe et al. 2019). Rarely, some patients showing MEN1 clinical characteristics do not present *MEN1* gene mutations, a condition that has been named MEN4 (Pepe et al. 2019). These patients are affected by primary hyperthyroidism that is isolated or associated with gastroenteropancreatic NETS and pituitary adenomas.

Carney complex is a rare multiple neoplasia syndrome. This syndrome is autosomal, is dominantly inherited, and is characterized by the presence of endocrine and non-endocrine tumors, including pituitary adenomas, pigmented lesions of the skin, and cardiac and cutaneous myxomas. In Carney complex, the most common endocrine manifestation, which often occurs often in females and may be able to alter the reproductive system, is ACTH-independent Cushing syndrome due to primary pigmented nodular adrenocortical disease (Pepe et al. 2019). 75% of patients affected have thyroid follicular adenomas and elevated GH and IGF-I, often with associated hyperprolactinemia. The genetic background of Carney complex is mostly due to heterozygous inactivating mutations in the *PRKAR1A* gene coding for the regulatory subunit type 1 alpha of the protein kinase A (PKA), leading to increased cAMP-dependent PKA activity which drives tumor formation in tissues of the affected patients.

McCune-Albright syndrome is a rare disorder characterized by polyostotic fibrous dysplasia, café-au-lait skin macules, and endocrinopathies that affect the reproductive system and the ovarian function, mainly in adolescents (Sotomayor et al. 2011). It arises from post-zygotic somatic activating mutations in the *GNAS* gene, encoding the cAMP-regulating transcript α-subunit Gsα and then producing a constitutive Gs signaling which results in activation of adenylyl cyclase and dysregulated cAMP production. A pituitary involvement, mainly with GH excess, is present in about 20% of patients affected, often associated with hyperprolactinemia and menstrual dysfunction, with the age of onset being around 24 years. In patients with hereditary pheochromocytoma and paraganglioma due to germline heterozygous mutations in gene encoding dehydrogenase subunits and the SDH complex assembly factor 2 protein (*SDHAF2*), the development of pituitary tumor, mainly prolactinomas and GH-secreting adenomas, has been described. The

DICER1 syndrome, a rare autosomal dominant disorder due to germline heterozygous mutation in the *DICER1* gene, is characterized by the onset of different kinds of malignant and benign tumors, including ovarian sex cord-stromal tumors, cystic nephroma, differentiated thyroid cancer, pituitary blastoma, genitourinary embryonic rhabdomyosarcoma, and pineaoblastoma. These are disorders that may all deeply affect the reproductive system in females (Pepe et al. 2019; Caimari and Korbonits 2016).

To summarize, while most pituitary adenomas occur sporadically, some of them, about 5%, may occur in a familial setting as a result of genetic germline or somatic mutations of pituitary adenoma-predisposing genes, either isolated like FIPA or as a part of a syndrome. A modification of local expression of growth factors and reproductive hormone receptors could have a role in determining the tumor level, resistance to treatment, and a worse prognosis.

A functional anterior and posterior pituitary deficiency inducing menstrual disorders may be due to hypophysitis, an acute or chronic inflammation of the pituitary gland. Hypophysitis can be classified according to etiology, morphology, and/or histopathology. Primary hypophysitis refers to isolated inflammation of the pituitary that is not associated with drugs, infections, or other disorders, while secondary hypophysitis may be due to medications targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed cell death 1 (PD-1), rupture of Rathke's cyst, craniopharyngiomas, and hemorrhagic pituitary adenomas. Patients affected have symptoms related to mass effects from pituitary gland enlargement and pituitary dysfunction. The dominant symptom is severe headache together (less frequently) with visual symptoms due to compression of the optic and/or cranial nerves. Patients display multiple anterior pituitary hormone deficiencies often not related to the MR findings, without a clear hierarchy, as are observed in clinically nonfunctioning adenomas (Faje 2016).

Menstrual Disorders and Adrenal Pathologies

The adrenal gland integrates two embryologically distinct endocrine systems within one organ capsule, the cortex, producing steroid hormones, and the catecholamine-producing medulla. The adrenal cortex, arranged in the outermost zona glomerulosa secreting mineralocorticoids (aldosterone), the zona fasciculata producing glucocorticoids (cortisol), and the zona reticularis which produces androgens (testosterone and dehydroepiandrosterone sulfate), is mostly regulated by ACTH produced in the anterior pituitary corticotroph cells, whereas the adrenal medulla releases catecholamines in response to the activated sympathetic nervous system (SNS). An increased adrenal cortex production of DHEAS may cause hyperandrogenemia and an impaired menstrual cycle and fertility (Ross and Louw 2015).

Cushing syndrome, which may occur in young women, is an important cause of loss of menstrual cyclicity and infertility. Cushing syndrome may be ACTH-dependent, with the ectopic production of ACTH or CRH by carcinomas or neuroendocrine tumors, or ACTH-independent, caused by unilateral adenomas or carcinomas

of the adrenal gland. The hypersecretion of cortisol causes lipolysis and fat redistribution together with loss of muscle mass and bone and skin disorders. Central obesity is a paradigmatic clinical manifestation of hypercortisolism. Cortisol excess can be subtle in an early stage of the disease and its diagnosis may be missed or even confused with a metabolic syndrome. In a retrospective study performed on women affected with Cushing syndrome during the reproductive period, many of them had been diagnosed as having solely a polycystic ovary syndrome, so testing for hypercortisolism in all women with suspected PCOS is suggested (Brzana et al. 2014). A history of hirsutism with rapid onset or clinically objective elements directing a hypercortisolism, such as thin skin, proximal muscle weakness, and central obesity, should promptly activate screening aimed at excluding Cushing syndrome. To be confirmed, a diagnosis of Cushing syndrome provides the measurement of plasma ACTH that will determine if the disease is ACTH-dependent or ACTH-independent. Where ACTH values <5 pg/mL are highlighted, an ACTH-independent Cushing syndrome can be diagnosed, and an abdominal computer tomography needs to be performed. If the ACTH plasma levels are normal or elevated, a magnetic resonance imaging of the pituitary with gadolinium contrast must be programmed.

The adrenal gland is a key component of the stress system in the human body. Multiple endocrine, paracrine, and intracrine interactions between different cell types within the adrenal gland microenvironment are supported by high vascularization and the activity of the adrenal cortex extracellular matrix (Kanczkowski et al. 2017). Obesity, sepsis, metabolic syndrome, and diabetes, besides several conditions of latent stress, may alter the adrenal gland microenvironment, activating the chronic hypersecretion of glucocorticoids and catecholamines that exert different systemic actions ultimately finalized to the restoration of body homeostasis.

Not only patients with Cushing syndrome but even those suffering from Conn syndrome due to hyperaldosteronism have an increased risk of developing metabolic syndrome, depression, osteoporosis, and cardiovascular diseases. The adrenal gland has a high regenerative capacity and the ability to adapt to various physiological and pathological conditions through complex bidirectional interactions between the cortex and medulla. Females under acute or chronic psychological stress, and with chronic overproduction of glucocorticoids and catecholamines, may experience a constellation of neuroendocrine changes and may develop menstrual disorders and amenorrhea due to stress-induced suppression of gonadotropin-releasing hormone pulsatile secretion by the activated hypothalamic-pituitary-adrenal axis (Stephens et al. 2016).

ACTH release is required by the body at basal, circadian, and stress-induced levels. When the plasma cortisol levels are lower than required, ACTH rises. Therefore, in the case of adrenal enzyme deficiencies that cause impaired synthesis and reduced cortisol secretion, the chronic elevation of ACTH induces overstimulation of the adrenal cortex. This condition occurs in the case of congenital adrenal hyperplasia (CAH), a group of diseases which develop as a result of a deficiency of enzymes or cofactor proteins required for cortisol biosynthesis (Speiser and White 2003). When we consider the functional defect in the cortisol synthesis,

the negative feedback at hypothalamic and anterior pituitary levels decreases leading to an increase in plasma ACTH and, consequently, to adrenal hyperplasia. CAH is mostly caused by mutations in the *CYP21A2* gene and classified as classic and non-classic types. The classic type arises from severe impairment of the activity of the enzyme 21 hydroxylase which belongs to the cytochrome P450 superfamily encoded by the *CYP21A2* gene which can be suspected in infants born with ambiguous genitalia as simple virilizing or as the most severe salt-wasting type. In the case of non-classic congenital adrenal hyperplasia (NCCAH), genital virilization is not observed at birth, whereas premature adrenarche/pubarche and menstrual irregularities in the post-pubertal period are commonly described. NCCAH includes clinical conditions due to gene mutations or disorders in the steroid synthesis steps of the steroidogenic acute regulatory protein (StAR) that provides the transfer of cholesterol from the mitochondrial membrane to the cell. Therefore, NCCH differs significantly from CAH because it has a later and dissimilar clinical expression.

The most common forms of NCCAH are observed in 21- and 11β-hydroxysteroid dehydrogenase (OHSD) deficiencies which are manifested in hirsutism, clitoromegaly, acne, alopecia, and menstrual irregularities like oligomenorrhea and anovulation, conditions often confused with PCOS. In these cases the assay in the early morning (8 a.m.) during the follicular phase (between the third and the seventh post-menstruation days) of 17αOH progesterone levels and the determination of its levels after the i.v. administration of cortrosyn (ACTH) 250 μgr are considered the gold standards for diagnosis. A basal 17αOH progesterone concentration $>$ 2 ng/mL and plasma levels 60 minutes after intravenous ACTH $>$10 ng/mL may be in agreement with the results of genetic studies that characterize the syndrome. In the case of basal levels of 17αOH progesterone $>$10 ng/mL, a non-classic 11β-hydroxysteroid dehydrogenase deficiency may be suspected which can be confirmed by 11-deoxycortisol levels $>$18 ng mL after ACTH test and genetic studies. A non-classic 3β-hydroxysteroid dehydrogenase deficiency can be diagnosed if basal 17OH pregnenolone levels are $>$30 ng/mL together with 17OH pregnenolone/cortisol ratio $>$ 10SD and clinical symptoms of the androgen excess syndrome.

In late-onset non-classic CAH diagnosed in adults, as in the classic CAH form in the newborn, clinical genetic counseling and genetic testing for mutations in the *CYP21A2* gene on DNA from peripheral blood cells are needed. As observed above, the *CYP21A2* gene is located on the short arm of chromosome 6 (6p21.3) mapped in a duplicate locus within the human major histocompatibility complex (MHC) where it lies in close proximity to a high homologous pseudogene – *CYP21A1P* – arranged in tandem repeats with the genes encoding the fourth component of complement (*C4A* and *C4B*). The tenascin (*TNX*) and serine threonine nuclear protein kinase (*RP*) genes are also located in this region, and four genes (*CYP21A2*, *RP*, *C4*, and *TNX*) form a unit called the RCCX (Carmina et al. 2017). The RCCX modules display a high degree of sequence homology so that a misalignment of sister chromatids during mitosis can result in gene conversion where a small part of one sister chromatid is copied to the other (M New). Therefore, a sequence of the *CYP21A2* gene may be copied to the *CYP21A1P* gene and vice versa, and a large range of gene deletions can take place in the RCCX module. The patient's phenotype is usually

determined by the milder affected allele, and then at least one mildly affected allele is present in non-classic CAH, with a good correlation between the severity of the clinical disease and the mutations observed.

As far as the fertility of females affected with NCCAH is concerned, they have been shown to be more likely to became pregnant compared to females with classic CAH. The condition of chronic high androgen levels is responsible for chronic oligo-anovulation in the presence of high plasma concentrations of progesterone due to the enzyme defect which may alter the endometrial intracrine function and impair implantation. Women with CAH may have impediments to fertility for anatomical reasons as well, such as vaginal stenosis or dyspareunia which make it more difficult to have intercourse. Endogenous glucocorticoids that suppress the hypothalamic corticotrophin-releasing hormone (CRH) may restore ovulation and fertility. The bedtime administration of dexamethasone at variable doses between 0.25 and 1 mg is considered the most effective regimen for ACTH suppression. If fertility is not desired, oral contraceptives (OCs) rather than glucocorticoids are suggested for menstrual cycle management. OCs suppress ovarian androgens, ACTH, and adrenal androgens, and therefore they appear to be more effective in the treatment of androgen excess, with which the majority of CAH patients are affected.

Menstrual Disorders and Thyroid Diseases

Thyroid diseases may have adverse effects on female reproduction. Understanding thyroid physiology and the impact that thyroid hormones may have on the female reproductive machinery help to understand the still unclear relationship between thyroid function and menstrual physiology. A recent study on a longitudinal cohort of premenopausal women recorded that thyroid hormone levels within the euthyroid range were associated with several menstrual cycle function outcomes. In particular, 3,3′,5,5′-tetra-iodothyronine (T4) and 3,5,3′-tri-iodothyronine (T3) were positively related to urinary estrogens and progesterone metabolites across the menstrual cycle (Jacobson et al. 2018). The morphofunctional unit of the thyroid gland is represented by the thyroid follicle where thyroid hormones are synthesized and stored. The thyroid follicle is made up of bipolar secretory epithelial cells with their basal membrane expressing the TSH receptor and sodium/iodine symporter and the apical membrane where the thyroid peroxidase (TPO) and pendrin (involved in the active transport of iodine) are located. The follicular cells synthesize thyroglobulin (TG), a large tyrosine-rich protein that contains about 10% carbohydrate. They surround an internal cavity containing colloid where huge quantities of TG and thyroid hormones are stored. Iodide uptaken by blood is concentrated in colloid and used for the iodination of tyrosine residues present on the TG backbone so that, even with the action of TPO, the inactive precursors mono- and diiodotyrosines are produced, stored, and used for the synthesis of 3,5,3′-tri-iodothyronine (T3) and 3,3′,5,5′-tetra-iodothyronine (T4) – the two active thyroid hormones.

Plasma thyroid hormones circulate within a range controlled through a negative feedback loop on TRH at the hypothalamic level and TSH secreted by the thyrotroph cells of the anterior pituitary gland. Beyond the hypothalamic-pituitary-thyroid axis, the concentrations of thyroid hormone binding globulin (TBG), transthyretin, and albumin, in different proportions, regulate the circulating T4. TBG binds approximately 70% of the circulating T4. During pregnancy, estradiol induces a rise in liver TBG glycosylation, and the increased binding capacity of this protein can transiently decrease free T4 concentrations leading to an increase in the plasma levels of TSH and total T4. Active thyroid hormones affect all the tissues and cellular processes and are critical for normal development, growth, metabolism, adrenergic interactions, thermogenesis, and metabolic influences on the central regulation of the thyroid axis (Mullur et al. 2014). They bind specific thyroid hormone receptors (THRs) – members of the superfamily of hormone-responsive nuclear transcription factors – that are encoded by the thyroid hormone receptor α (*THRA*) and the thyroid hormone receptor β (*THRB*) genes. The *THRA* gene is located on human chromosome 17 and transcribes three THR isoforms, the THRα1, which binds T3 and may form dimers with other truncated proteins, the THRα2 and the THRα3, whose physiological importance is still not completely understood even if their heterodimerization with the full-length THR proteins seems to antagonize the T3-mediated transcriptional activation (Gauthier EMBO J). The *THRB* gene is located on human chromosome 3 and codifies for the T-3 binding isoforms THRβ1 and THRβ2 (a third isoform THRβ3 has been detected only in rats).

Therefore, the isoforms TRHα1, THRβ1, and THRβ2 are the main mediators of thyroid hormone action and have different tissue distribution as indicated by the clinical phenotype of patients with mutations and resistance to thyroid hormones (Gauthier et al. 1999). THRβ isoforms are the predominant receptors expressed in the liver and cardiac ventricles, whereas TRHα1 is preferentially expressed in the brain, heart atria, and white adipose tissue; brown adipose tissue expresses both THRα and β. Both THRα and β undergo posttranslational modification by sumoylation, which is essential for positive and negative gene regulation by thyroid hormones (Ortiga-Carvalho 2014). THRs form a heterodimer complex with the retinoid X receptor (RXR), binding to thyroid response elements (TRE) of the target cell DNA. The intracellular conversion of thyroxin to the active form – triiodothyronine – is the key intracrine mechanism of thyroid hormone action. This is provided by the iodothyronine deiodinase, deiodinases 1 (D1) and 2 (D2), activating enzymes, and deiodinase 3 (D3), an inactivating enzyme, which are all differentially expressed in mammalian tissues. D2, expressed in key thyroid-responsive tissues such as the brain, skeletal muscle, and brown fat, is the enzyme mostly responsible for the intracytoplasmatic increase in T3 which, when transferred to the nucleus, regulates gene transcription.

To summarize, if we have to consider the relationship between thyroid diseases and menstrual disorders, we cannot ignore the molecular mechanisms of thyroid hormone secretion and action modulated by the systemic hypothalamic-pituitary feedback, the plasma transport, nutrient feedback at a central and local level, the signaling pathways, and the intracrine cellular regulation (Colicchia et al. 2014).

Thyroid hormones and their receptors are present in the endometrium, and their expression changes during the menstrual cycle. TRHα1 and THRβ1 have both been described in the mid-luteal phase in glandular and luminal epithelium, showing an increase during the secretory phase and a subsequent dramatic decrease. It has also been demonstrated that transcripts in thyroid hormone synthesis and action, such as NIS, thyroglobulin, deiodinases, and thyroid peroxidase (TPO), are expressed in the endometrial epithelium (Colicchia et al. 2014). This suggests the hypothesis of a local controlled production and action of thyroid hormones at the endometrial level and emphasizes the correlations between the importance of normal thyroid function and regular menstrual flow.

Testosterone seems to be necessary for the transcriptional regulation of factors involved in THR expression and may explain the menstrual abnormalities and subfertility in women with primary hypothyroidism. Thyroid hormones have been assayed in human follicular fluid, and both granulosa and ovarian stromal cells express THRs. The expression of TRHα1, THRβ1, and THRβ2 in mature oocytes from patients subjected to in vitro fertilization suggests that the human female gamete could be directly responsive to T3, probably influencing its maturation and the secretion of hyaluronic acid which causes the pre-ovulatory cumulus expansion. However, in the mouse model, a direct thyroid hormone action on the process of cumulus expansion and meiotic maturation has been not observed, and TSH or T4 added in vitro to cultured human ovarian tissue has no effect on the development of follicles (Colicchia et al. 2014), even if they potentiate FSH-induced granulosa cell survival by inhibiting cell apoptosis and promoting cell proliferation. To summarize, thyroid hormones, which act on their specific receptors expressed by ovarian granulosa cells and oocytes at different stage of follicular maturation, seem to influence granulosa cell survival and steroidogenesis.

Both hypothyroid and hyperthyroid women have been reported to experience a greater prevalence of menstrual irregularities compared with euthyroid women (Koutras 1997). Hypothyroidism deeply alters ovarian function and ovulation. It induces a decreased metabolic clearance rate of androstenedione and estrone, reduced binding activity of SHBG, and an increasing of 17βestradiol and testosterone unbound fractions associated with increased prolactin plasma concentrations. These changes are reported to alter the length of the menstrual cycle and the amount of menstrual bleeding, such as oligomenorrhea, amenorrhea, polymenorrhea, and menorrhagia, therefore inducing anovulation and alteration in the female reproductive system (Krassas et al. 2010). In particular, hypothyroid women are more likely to experience hypomenorrhea compared with normal women, although most of the clinical reports compare women with severe hypothyroidism and myxedema to euthyroid women without taking into account the correlation with thyroid hormone plasma levels.

If we want to consider clinical studies performed as a whole, hypothyroid women experience a frequency of menstrual disturbances that is almost three times greater compared to the normal population (Kakuno et al. 2010). A separate note of interest relates to the presence in the serum of thyroid autoantibodies that may or may not be associated with reduced circulating thyroid hormone levels and seems not be related

to the development of menstrual abnormalities. The presence of an association between subclinical hypothyroidism, serum antithyroid autoantibodies, and infertility has been broadly assessed in several studies. Many authors consider subclinical hypothyroidism an infertility factor in women, a factor that is reversed by treatment with small doses of levothyroxine in order to improve the corpus luteum function. Overall, the studies correlate the plasma levels of TSH with female infertility, demonstrating that mean circulating TSH is significantly higher in infertile patients compared to control patients, even if TSH plasma levels higher than the normal range are not prevalent in infertile women (Jokar et al. 2018). Thyroid autoimmunity, which is often not diagnosed, is an endocrine disorder that is up to ten times more common in women than men. It has been related to reproductive failure, and many studies have investigated the association between thyroid autoimmunity, menstrual disturbances, and female infertility, even if the interpretation of the data is difficult due to the heterogeneity of the subject samples studied, a lack of controlled and retrospective studies, sample sizes, and the laboratory methods used.

A study conducted on a large number of women to examine the relationship between low ovarian reserve and thyroid autoimmunity failed to demonstrate a prevalence of positive thyroid autoantibodies among women with low, normal, or high anti-Mullerian hormone (AMH) levels. However, analyzing only the results obtained from women with low AMH, the authors observed a significantly higher prevalence of overt and subclinical hypothyroidism in the group with a genetic cause for low ovarian reserve (Polyzos et al. 2015). The presence of thyroid autoimmunity in women affected with PCOS has also been investigated. The studies performed revealed a higher serum evidence of thyroid antibodies, more hypoechoic areas on thyroid ultrasound, and higher mean TSH values in women with menstrual disturbances and PCOS compared to controls. This observation indicates the prevalence of autoimmune thyroiditis in women with PCOS that is threefold greater than controls, establishing a relationship between the incidence of positive auto-antibody and female infertility. Subclinical hypothyroidism and autoimmune thyroid disease have been associated with recurrent miscarriage, although the pathogenetic mechanisms and the benefit from treatment with levothyroxine are still debated.

A large number of studies over the last 20 years in the area of thyroid and pregnancy have established that the presence of thyroid autoimmunity is associated with a significant increased miscarriage risk (Lazzarin et al. 2012; Zhang et al. 2017). For this reason, the Thyroid Endocrine Society (*TES*) and the American Thyroid Association (ATA) suggested that the specific ranges for TSH in the early, middle, and late stages of pregnancy should be considered, respectively, 0–2.5 mIU/L, 0.3–3.0 mIU/L, and 0.3–3.0 mIU/L. This is a recommendation that has been adopted by the international community. A more recent meta-analysis emphasized that subclinical hypothyroidism is a risk factor for miscarriage in women before 20 weeks of pregnancy and that early treatment with levothyroxine to keep plasma TSH levels below 2.5 mIU/L can reduce the miscarriage (Zhang et al. 2017). Furthermore, a retrospective study on the association between thyroid autoantibodies with β2-glycoprotein and cardiolipin antibodies as etiological factors for recurrent miscarriage revealed that high levels of ABTPO were positively correlated with IgG

antibodies, suggesting antiphospholipid syndrome and highlighting the importance of considering the association of thyroid autoimmunity with other important autoimmune diseases in women with recurrent miscarriage (Unuane et al. 2017). In contrary fashion, other studies claim that subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, early pregnancy loss, and live birth, so that women affected can be reassured that their chances of conceiving and achieving a live birth are likely to be unaffected by subclinical thyroid dysfunction (Plowden et al. 2016).

Women affected with hyperthyroidism present clinical symptoms of weight loss, palpitations, anxiety, increased bowel motility, and menstrual irregularities. Although menstrual cycle length, modification of the follicular and luteal phases, bleeding length and intensity, oligomenorrhea, and amenorrhea are more common in women with hyperthyroidism than in euthyroid women, there is less evidence of ovulatory dysfunction and infertility compared to what occurs in hypothyroidism, as discussed above. The most common causes of thyrotoxicosis is the Graves-Basedow disease, an autoimmune disease in which the thyroid stimulating immunoglobulin (anti-TSH receptor antibodies) leads to the unregulated stimulation of thyroid hormone production with associated orbitopathy and ophthalmopathy. Other causes of hyperthyroid function, overt or subclinical, can be an autonomous thyroid nodule and a multinodular goiter. Overall, these conditions induce thyrotoxicosis (elevated free T4 and low plasma TSH) that leads to increased serum levels of SHBG and hyper-estrogenism during all phases of the menstrual cycle and consequently to increased free estrogen levels. In hyperthyroid women, changes in androgen metabolism also occur with increased plasma levels of testosterone and androstenedione and a modified androstenedione-to-estrone ratio. The mean LH levels in both the follicular and the luteal phases of the menstrual cycle are higher, whereas the pulsatile LH and FSH secretion does not differ in hyperthyroid women compared to controls. Amenorrhea has been frequently reported as associated with hyperthyroidism, as well as various other menstrual cycle changes including oligomenorrhea, hypomenorrhea, and anovulation, and these irregularities may sometimes precede the identification of thyroid dysfunction.

To summarize, both hyper- and hypothyroidism may have adverse effects on the menstrual cycle, mainly hypomenorrhea and polymenorrhea in the case of hyperfunction and oligomenorrhea in the case of hypofunction. These endocrine disorders characteristically induce changes in SHBG and sex steroids, and the early diagnosis of their overt, subclinical, and mild expressions may reduce the incidence of menstrual abnormalities.

Conclusion

Almost all the endocrine diseases may cause irregularities of the menstrual cycle defined by modification of its length, frequency, and pattern of blood loss. In this chapter, I have mainly focused on neuroendocrine and pituitary dysfunctions and on adrenal and thyroid disorders because, when clinically symptomatic, they may be

emblematic of important changes in the dynamic activity of the endometrium. These endocrine disorders are associated with disturbances in the central regulation of the hypothalamic-pituitary axis and morphological changes within the uterus. The most frequent and important endocrine causes of menstrual abnormalities may be attributed to primary or secondary ovarian failure and PCOS. Overt and latent adrenal and thyroid diseases are associated with irregularities in the pattern of the menstrual cycle that may reflect disturbances in the local endometrial environment. A modification of the local availability of prostanoids or other angiogenic-permeability factors may activate receptor signaling and downstream modify the regulation of the gene transcription of angiogenic and anti-angiogenic factors, inducing thereby menstrual dysfunctions. The genomics and proteomics approaches will enhance the possibility of better understanding how endocrine disorders may modify the peripheral tissue metabolism of steroids. In fact, several endocrine diseases could modify the endometrial expression of enzymes that play important roles in the activation and inactivation of estrogens and androgens and their specific receptors. The identification of the intra-tissue concentrations of steroids by liquid chromatography-tandem mass spectrometry (LC-MS/MS) during endocrine disorders will be an important tool in having a better understanding of the role of cyclic steroid changes within the endometrium.

Cross-References

- ▶ Diagnostic Protocols for Infertility
- ▶ Endocrinology of Maternal-Placental Axis
- ▶ The Hypothalamus-Pituitary-Ovary Axis
- ▶ The Menstrual Cycle and Related Disorders
- ▶ The Menstrual Disorders Related to Systemic Diseases
- ▶ The Polycystic Ovary Syndrome (PCOS)

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