MANAGEMENT OF ENDOCRINE DISEASE

Female sexual dysfunction for the endocrinologist

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Abstract

Sexual function is an important component of either general health and quality of life in both genders. Many studies have focused on the different risk factors for sexual dysfunctions, proving an association with several medical conditions. Endocrine disorders have been often mentioned in the pathogenesis of female and male sexual dysfunctions; however, particularly in women, sexual function is rarely addressed during clinical, in general, and endocrinological, in particular, consultations. As a thorough diagnosis is required in order to provide an adequately tailored treatment, knowing how each endocrine dysfunction can impair sexual health is of the utmost importance, considering the high prevalence of conditions such as disorders of pituitary, thyroid, adrenal, gonads, as well as metabolic disorders. We performed a thorough review of existing literature on the different mechanisms involved in the pathogenesis of female sexual dysfunctions secondary to endocrine disorders in order to provide an up-to-date reference.

European Journal of Endocrinology
(2020) **182**, R101–R116

Introduction

Gender development, sexual anatomy, and function, as well as sexual behaviors, are largely hormone-dependent characteristics of human beings. However, unfortunately and surprisingly, the presence of the endocrinological science in the new, but growing, field of medical sexology/

sexual medicine is unfortunately not fully developed yet (1). The presence of endocrine disorders in the principal sexual dysfunctions is rarely searched, just as the presence of sexual dysfunction (SD) in endocrine and metabolic diseases (2) is rarely investigated. In clinical practice, little

Invited Author's profile

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consideration is given to the evaluation of sexual function during endocrine disorders. This is particularly evident, but really puzzling and not easy to understand, in women (3), whose sexuality is exquisitely and dramatically hormone-dependent in all the phases of their life. While several studies have shown the association of sexual dysfunctions (SD) with endocrine disorders, the exact prevalence of this comorbidity cannot be easily assessed, as there are no studies from random, population-based samples. However, these disorders are common, quite dramatically impacting both, in general, quality of life (QoL) and the sexual QoL (SQoL) and often easily treatable.

In this review, we have analyzed the publications concerning the sexual function of women affected by pituitary, thyroid, adrenal and gonadal disorders, as well as metabolic diseases (Fig. 1). As a methodological screening, we decided to concentrate mainly in the studies addressing female sexual function through a popular, well validated psychometric tool, such as the Female Sexual Function Index (FSFI) in its full (4) or abridged form (FSFI-6) (5).

Search strategy

A literature search was conducted using PubMed, Cochrane, Embase, and Scopus database, using the following terms with the Boolean operators AND and OR: prolactin, hyperprolactinemia, prolactinoma, growth hormone, GH, IGF1, thyroid, hypothyroidism, hyperthyroidism, thyroid

disease, goiter, Graves, Basedow, Hashimoto, adrenal, glucocorticoid, mineralocorticoid, cortisol, DHEA, Cushing, Addison, hypercortisolism, hypocortisolism, congenital adrenal hyperplasia, CAH, hypoaldosteronism, hyperaldosteronism, adrenal failure, hyperandrogenism, hypogonadism, Turner, estrogen deficiency, testosterone deficiency, hyperandrogenism, androstenedione, diabetes, gout, hyperuricemia, FSD, female sexual dysfunction, vaginismus, vaginal dryness, dyspareunia, hypoactive sexual desire disorder, HSDD, FSFI, female sexual function index, quality of life, QoL, sexual quality of life, SQoL. Literature search was conducted independently by two Authors (E C and A S) between August and October, 2019.

Prolactin

The link between prolactin (PRL) levels and sexual function is well known. A transient increase in serum PRL is observed both in men and women in many eustressing and distressing activities and, specifically, after the orgasm (6), probably partly accounting for the refractory period (7).

Hypoprolactinemia

While the correlation between low levels of PRL and male SD has been investigated, such as in premature ejaculation (8, 9), similar studies do not exist in female.

Hyperprolactinemia

It is well known that chronically elevated PRL levels induce a reduction of sexual activity in animals and are associated with hypoactive sexual desire disorder (HSDD) in men and women (10). For such reasons, PRL has been suggested as a peripheral biomarker of sexual and reproductive dysfunction (11). Solid evidence confirms, in fact, the inhibitory effect of prolactin on gonadotropin secretion and on the dopaminergic pathway, the main central regulator of desire and arousal, thus reducing these behavioral parameters (12). While the majority of studies on the effect of chronic hyperprolactinemia on reproductive functions have focused on female patients, given the higher prevalence in women than in men, they have mainly focused on gonadal and reproductive function rather than to sexual health (11). In men, the effects of hyperprolactinemia are partly mediated through inhibition of the hypothalamic-pituitary-gonadal axis, but some evidence also suggests that a direct effect is

Figure 1

Endocrine alterations associated with impairment of sexual health and sexual function in women.

found on sexual desire (13). Despite lacking evidence in these regards, the same mechanisms could theoretically provide additional explanation for impaired sexual health in affected women. Sexually dysfunctional women with hyperprolactinemia are largely underestimated by the physician as well by many endocrinologists. Few studies on this topic have been published so far (Table 1), showing that women with hyperprolactinemia have lower FSFI score test than controls (14, 15, 16) and that treatment with dopaminergic drugs commonly used in different forms of hyperprolactinemia significantly improves FSFI total score and all domain scores (16, 17). All studies came to the same conclusion, despite small sample size, therefore reinforcing the correlation found by Krysiak and colleagues (16) between prolactin levels and the severity of SD in women. Curiously, Krysiak and colleagues also investigated the extent of SD in patients with macroprolactinemia and found that, while all domains of the FSFI were affected by 'common' hyperprolactinemia, sexual desire was the only one negatively affected by macroprolactinemia (15). This is hardly adequate evidence to suspect a causative role for macroprolactinemia in SD; however, more recently, Kalsi and colleagues reported that macroprolactinemia was also frequently associated with reproductive dysfunctions, although sexual function was not investigated via the FSFI (18). Based on these premises, it should therefore be clear that sexual function should be investigated in all cases of hyperprolactinemia, not just in women of reproductive age. For the same reasons, prolactin should always be assessed as a first-line investigation for women complaining of all kinds of sexual dysfunctions.

Growth hormone

It is textbook knowledge that growth hormone (GH) is responsible for regulation of linear growth during childhood; however, GH also exerts several actions during the entire life, regulating protein, glucose, and lipid metabolism, as well as cardiovascular and other systems functions. GH is also supposed to be involved in the regulation of sexual functions: in fact, GH receptors are located in both male and female gonads and genitalia (19, 20), including the oocyte, granulosa, and testicular cells.

Decreased GH

So far, no study has adequately addressed the effects of both GH-dependent and non-GH-dependent dwarfism

Table 1 Studies reporting hyperprolactinemia (HyperP) and female sexual dysfunction (FSD).

Studies	Patients		Scores			P	Comments
	n	Age	FSFI	CTRL	HyperP		
14	HyperP = 25	35.72 ± 10.2	FSFI	31.10 (27.55–32.88)	HyperP + Bromo	<0.0001	SD was diagnosed in 88% patients, while only 25% of CTRL women were found to have SD. All FSFI domains scores were lower in women with HyperP. The most affected domains were desire and arousal.
	CTRL = 16	34.86 ± 4.88					
15	HyperP = 14	30 ± 5	FSFI	31.67 ± 3.15		<0.05	Women with HyperP had lower total scores on the FSFI than control subjects. All FSFI domains scores were lower in women with HyperP. Small sample.
	CTRL = 14	29 ± 5					
17	HyperP = 15	32 ± 5	FSFI	32.37 ± 2.18 vs	27.64 ± 2.39 vs	<0.05	Women with HyperP had lower total scores on the FSFI than control subjects. Bromo treatment significantly increase FSFI total score and all domain scores. Small sample.
	HyperP + Bromo = 15	32 ± 6		32.25 ± 2.40*	27.19 ± 2.61*		
	CTRL = 14	30 ± 6					

*T0 vs 3 months.

Bromo, bromocriptine; CTRL, controls without hyperprolactinemia; FSFI, Female Sexual Function Index; SFV, sexual function valuation.

on female sexual function. We are currently trying to fill this gap, being evident that hypostature must affect the relational and intrapsychic life and, as a consequence, the SQoL itself. It is safe to assume that dwarfism, even in its less severe forms, can become a psychological burden to affected subjects; additionally, GH deficiency in adults is also associated with reduced strength, depressed mood, and fatigue (21) – all symptoms which can worsen sexual health and impair sexual function.

Increased GH

Increase of GH and IGF-1 is a clinical condition that can be found in gigantism, when occurring in childhood, and in acromegaly, when occurring in adulthood. The main clinical features of acromegaly are change in somatic features, extremity enlargement, soft tissue swelling, and visceromegaly; additionally, metabolic alterations like diabetes are common. Acromegaly has an important diagnostic delay, as symptoms often overlap with more common disorders. Early diagnosis is therefore of the utmost importance, as changes in appearance may not be reversible, even with successful treatment. Acromegaly is associated with severe impairment of quality of life, dissatisfaction of body image, and tendency to social isolation that can be a cause of SD in itself (10). A single study has investigated female sexual function in acromegaly patients (22) using FSFI. SD was present in 68% of patients with acromegaly compared to 28% of healthy women, and all FSFI domains scores were significantly lower in acromegalic patients than among controls (22). Two groups were identified among patients with acromegaly: controlled and uncontrolled acromegaly, according to serum GH and IGF1 levels during treatment. No significant difference was found between biochemically controlled and uncontrolled patients with respect to FSFI scores: this result does not confirm a direct involvement of GH on regulation of female sexual function. Although the FSFI total score was not different between controlled and uncontrolled acromegaly patients, regression analysis showed that the FSFI total score was associated with IGF-I levels. Symptoms of acromegaly tend to develop slowly, and therefore it does not seem surprising that many patients could attribute sexual dysfunction to any other different cause, such as sexual routine and advancing age. Regardless of the cause, endocrinologists should consider that SD is present in most patients with acromegaly and that it should, hence, be carefully investigated and addressed, even while undergoing specific treatments.

Thyroid

While the exact prevalence of hypo- and hyperthyroidism is unknown, it is generally assumed that thyroid dysfunctions are the most prevalent endocrine disorder. Both conditions, in fact, have a wide range of clinical manifestations, ranging from mild, hardly identifiable symptoms to overt, life-threatening crises (23, 24). Thyroid dysfunctions affect general health, as well as sexual health and SQoL. Although thyroid hyper- and hypofunctions are largely more present in women at all ages than in males, few studies using the FSFI have evaluated the effects of thyroid diseases on women's sexual function (Tables 1 and 2). Most of these studies were based on small, random, population-based samples derived from patient selected populations. Despite all these limitations, all studies show the association between thyroid disease and SD in women (25), confirming the same association found in men (26), although with different clinical impact. The prevalence of SD in hypothyroid women is around 22–46% (25, 27, 28), whereas it is higher – around 44–60% – in hyperthyroidism (29, 30, 31).

Hypothyroidism

All studies listed in Table 2 demonstrated a strong association between hypothyroidism and SD with a significant reduction of FSFI scores in hypothyroid women compared to controls (27, 28, 30, 31, 32). Different results are found in subclinical hypothyroidism: in fact, two studies performed on Asian women (33, 34) contradict the association between sub-clinical hypothyroidism and SD found by Atis (28). However, the authors do not provide solid explanations for this inconsistency, only stating that subclinical hypothyroidism fails to achieve the elevated TSH levels commonly reported in overt hypothyroidism which can induce hyperprolactinemia. Additionally, these two studies, both performed using the FSFI, do not consider levels of sex hormones or prolactin, therefore impairing reliability of the results.

Hyperthyroidism

In the last few years, different papers showed a correlation between hyperthyroidism and SD in women with case control studies (29, 30, 31, 35) (Table 3). Their major limitation is the fact that these are small studies, but they all showed the same result, therefore confirming the association between clinically-evident thyroid pathology and SD. The mechanism of action through which thyroid

Table 2 Studies concerning hypothyroidism (HypoT) and FSD.

	Patients, <i>n</i>				Scores				<i>P</i>	Comments				
	Reference	CTRL	HypoT	Sub-HypoT	Sub-HypoAU	Eu-Has	Method for SFV	CTRL			HypoT	Sub-HypoT	Sub-HypoAU	Eu-Has
32		36	24				FSFI; No SD >30; Middle SD: 23–29; Severe SD <23	30.3 ± 0.76	18.2 ± 2.41				<0.05	All FSFI domains are impaired in HypoT women respect to the controls. Small sample.
28		20	25	25			FSFI; SD <26.55	32.31 ± 3.50	23.92 ± 5.81	From 29.20 to 26.03			<0.001	All FSFI domains are impaired in HypoT women respect to the controls. Small sample.
30		30	17				FSFI		Single FSFI domains scores are lower in HypoT women				-	Direct correlation of FSFI scores and FT4 was observed in HypoT women. Small sample.
31		53	22				FSFI; SD <23.0	25.7 ± 5.2	20.7 ± 6.9				-	Compared with control, there was a significant decrease of desire, arousal and lubrication scores in HypoT women. Small sample.
33		948	138				FSFI; SD <26.55	23.8 (20.2–27.5)		24.4 (20.6–27.6)			No effect	Sub-HypoT is not a risk factor for SD in Korean women.
27		18	17	17	16		FSFI; SD <26.55	31.52 ± 2.75	27.87 ± 3.62	23.74 ± 4.00	27.98 ± 3.25		<0.05	Thyroid failure and autoimmunity is associated with SD. Small sample.
34		951	168				FSFI	25.7 ± 3.9		25.8 ± 3.9			No effect	Sub-HypoT is not a risk factor for SD in Chinese women.

CTRL, healthy euthyroid females without thyroid autoimmunity; Eu-Has, euthyroid women with Hashimoto's thyroiditis; FSFI, Female Sexual Function Index; SD, sexual dysfunction; SFV, sexual function valuation; Sub-HypoAU, women with autoimmune subclinical hypothyroidism; Sub-HypoT, nonautoimmune subclinical hypothyroidism.

Table 3 Studies reporting hyperthyroidism (HyperT) and FSD.

References	Patients, n			Scores				P	Comments
	CTRL	HyperT	Graves' disease	Toxic adenoma	Method for SFV	CTRL	HyperT	Graves' disease	Toxic adenoma
30	30	22			FSFI*				
29	40	40			FSFI; SD <26.55	29.0 ± 10.4	24.2 ± 9.96		
31	53	18			FSFI; SD <23.0	25.7 ± 5.2	19.5 ± 7.6		
35	34		31	30	FSFI; SD <26.55	32.03 ± 3.41	26.42 ± 3.89	28.85 ± 3.26	

*The FSFI's total scores have not been published for this study. SFV, sexual function valuation.

diseases induce SD is not known: the most reliable hypotheses are related either to the dysfunction of the hypothalamic thyroid axis which alters prolactin levels (25) or to a direct effect related to the levels of circulating thyroid hormones (30). This second hypothesis can be supported on the basis of the presence of thyroid hormone receptors in the genitals (36, 37).

Autoimmune thyroid disease

The issue of autoimmune thyroid disease is largely neglected by literature. Only a few studies, in fact, investigated whether thyroid autoimmunity – that is, thyroid peroxidase antibody serum titers – was associated with worse FSFI scores (27, 31). As these studies brought conflicting results, no definite consensus can be reached on the effects autoimmune thyroid disease has on female sexual function. Nevertheless, other studies using different questionnaires, such as the SF-36, highlighted that young women with autoimmune thyroid disease are more frequently self-reporting sexual health impairments, which they described as thyroid-related (38).

Adrenal gland

The adrenal gland is involved in the production and release of glucocorticoids, mineralocorticoids, and adrenal androgens. Different clinical scenarios are associated to impaired or exaggerated hormone release from different parts of the adrenal gland. More in detail, the adrenal gland is the major source for androgens in women (39), and it is therefore unsurprising that conditions resulting both impaired and exaggerated hormone release from the adrenal might influence female sexual health. This is true also for conditions not directly affecting androgen secretion from the adrenal, as glucocorticoids can interact with the androgen receptor and therefore elicit signaling response.

Adrenal insufficiency – Addison's disease

Primary, secondary, and tertiary forms of adrenal insufficiency are defined based on the source of dysfunction – the adrenal cortex, the pituitary gland, or the hypothalamus, respectively. Most cases of adrenal failure are currently attributed to either autoimmune adrenal disease or to drug-induced dysfunctions of the hypothalamic-pituitary-adrenal axis following long-term administration of glucocorticoids (40). Women affected

by primary or secondary adrenal insufficiency report a decrease of QoL compared with general population (41). Surprisingly, adrenal failures have rarely been correlated with the SQoL. Loss of libido has been reported in women with androgen insufficiency – a common feature of adrenal failure, given that almost 50% of androgen production in the female body stems from the adrenal (39). However, reports in these regards are inconsistent: in fact, Erichsen *et al.* assessed sexual function (using the Sexual Activity Questionnaire) in a cohort of women with Addison's disease and concluded that patients were as sexually active as healthy controls, with higher sexual pleasure and lower discomfort during intercourse. So far, no study has investigated sexual functioning in adrenal failure using the FSFI.

Adrenal insufficiency – hypoandrogenism

As previously stated, the adrenal is the most important source of androgen in the female, accounting for almost 50% of androgen production (39). The reduction of Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) in adrenal insufficiency can be associated with the presence of SD. In fact, DHEA and DEAS contribute substantially to the total sex hormone amount and biological activity in women by the conversion to testosterone and estrogen in peripheral tissues (42). Additionally, DHEA and DHEAS decline in older women (43) and replacement in normal elderly women has been associated with improvement of both QoL and SQoL (44). The effect of DHEA replacement was also studied on sexual function in women with contradictory results (Table 4). Arlt *et al.* demonstrated that adrenal insufficiency is associated to SD in sexually active women and that DHEA replacement therapy significantly reduced the comorbidity with SD with respect to placebo (45). However, other studies in older women (Table 4) did not confirm these results, suggesting that the adrenal hormone supplementations should be started as early as possible (46, 47).

Hyperandrogenism

Congenital and acquired adrenal hyperplasias or tumors have a large effect on female sexuality mostly through the consequent hyperandrogenism. Congenital adrenal hyperplasia (CAH) is a clinical syndrome, including features such as hyperandrogenism, hypocortisolism, and hypoaldosteronism resulting from 21-hydroxylase deficiency. Depending on the genetic background (the CYP21A2 genotype), two forms of CAH are commonly

Table 4 Studies concerning adrenal function and FSD.

Studies	Patients		Method for SFV	Scores		P	Comments
	n	Pl. vs DHEA, age		Parameters	Values		
Adrenal insufficiency							
45	24	23–59	Four VAS	Frequency of sexual thoughts Degree of sexual interest Mental satisfaction with sex Physical satisfaction with sex	27 ± 19 vs 42 ± 23 27 ± 20 vs 45 ± 22 36 ± 30 vs 55 ± 25 34 ± 29 vs 51 ± 26	0.01	The DHEA replacement therapy (50 mg) resulted in a significant improvement in SD and also in reduction of depression and anxiety after four months of treatment.
46	39	18–70	McCoy's SSQ	Desire Problems Satisfaction Fantasies Libido	8.3 ± 2.4 vs 8.3 ± 2.2 5.3 ± 2.3 vs 4.8 ± 2.9 19.2 ± 4.6 vs 18.8 ± 3.4 2.20 ± 0.43 vs 2.13 ± 0.45 2.27 ± 0.33 vs 2.20 ± 0.37	No effect	The DHEA replacement therapy (25 mg) does not have a major impact on subject health status or sexuality.
47	15	61.5 ± 1.7	ESF	Satisfaction Problems with lubrication Problem with orgasm Pain	3.07 ± 0.25 vs 3.20 ± 0.22 1.60 ± 2.60 vs 2.47 ± 0.36 1.70 ± 0.27 vs 2.10 ± 0.31 1.30 ± 0.21 vs 1.40 ± 0.16	No effect	The DHEA replacement therapy (50 mg) did not affect sexual functions
Cushing's Syndrome							
58*	29	30	FSFI		16.6 (5–23) 26.8 (25.5–30.4)	<0.0001	According to FSFI 24 women (88%) with Cushing had an SD

*Age: 34–42.

Pl, placebo; SFV, sexual function valuation; SSQ, sex scale questionnaire; VAS, visual-analogue scales.

reported: the classical form is more severe and manifests with salt-wasting crises and, in women, prenatal virilization of external genitalia; on the other hand the non-classical, late-onset form of CAH is clinically milder and is often discovered later in life (48). In both forms of CAH, both prenatal androgenization and masculinization of childhood behavior were associated, although to a minor extent, with bisexual/homosexual orientation (49). Classical CAH is also associated with disorders of sexual differentiation resulting in ambiguous genitalia and life-long psychosocial difficulties (50). Gastaud *et al.* have studied sexual function in classical CAH, suggesting that sexual function is severely impaired in these patients, with lower scores in all FSFI domains compared to healthy controls (51); likewise, Krysiak *et al.* have reported that women with non-classical CAH also had lower FSFI and higher BDI-II scores, suggestive of higher prevalence of sexual dysfunction and depression symptoms. More recently, Schernthaner-Reiter *et al.* compared the two forms of CAH, concluding that women with non-classical CAH have lower sexual function as well as higher sexual distress (48). Additionally, Gondim *et al.* (52) have reviewed observational studies on the sexual orientation of patients with CAH, reporting an increased prevalence of homosexuality and bisexuality among affected women compared to the general population. Although hypoactive sexual desire disorder (HSDD) is associated to lower androgen levels (53, 54), with data from clinical studies proving improvement of symptoms while undergoing treatment with transdermal testosterone (55, 56), little evidence from current literature supports the notion that hyperandrogenism from CAH could improve sexual health in affected patients.

In conclusion, a contemporary endocrinologist who is managing female patients with adrenal diseases without addressing sexual function with FSFI, at least in its abridged form, should consider the possibility to change his/her clinical habit in the interest of the patient's health.

Hypercortisolism

Exaggerated production of steroid hormones from the adrenal gland results in different clinical phenotypes, based on the kind of hormone produced. Excessive circulating levels of glucocorticoids result in Cushing's syndrome (CS) (57). Only a single study analyzed the presence of SD in the case of CS (58). This is a case control study that showed that women with CS had lower FSFI scores with respect to healthy controls, 24 (88%) out of 29 CS women had a SD. Moreover, arousal, lubrication,

orgasm, and satisfaction subdomains of FSFI were significantly lower in patients with CS. There is a positive correlation between FSFI scores and LH levels, supporting the hypothesis that SD may be correlated to the inhibitory effect of cortisol on sex hormones. We may hypothesize a direct effect of cortisol excess on other hormonal axes, on glucose metabolism, or on other systems. Moreover, the possibility that Cushing patients may have reduced sexual drive (despite a relative hyperandrogenism) and SQoL because of the specific alteration in the body image induced by the disease or by the syndrome is to be considered very likely.

Estrogen

Estrogen deficiency can have various causes: menopause, premature ovarian failure, Turner's syndrome, and hypothalamic pituitary disease. The effect of low estradiol levels results in vaginal dryness and dyspareunia, often accompanied by symptoms of vulvovaginal atrophy (50). These symptoms significantly contribute to the onset of sexual disorders. Estradiol is also a modulator of serotonergic function, affecting regions of the brain known to regulate mood and desire, which may also have effects on sexual function. The prevalence of SD in post-menopausal women is high, between 68% and 86% (59): menopause was, in fact, used as a model for exploring the effects of estrogen deficiency on sexual function. However, studying SD during menopause is complicated by the effects of aging and other related factors, like the general health status, the clinical and obstetric history, and the partner's sexual health (60, 61). Systemic or local treatment with estrogen induces statistically significant improvement of sexual functions when performed in women in early post-menopause (62). In 2017, Taylor analyzed the effect of estrogen therapy vs placebo in a 4-year prospective study on 727 postmenopausal women, obtaining the same result: a significant improvement of FSFI scores in estradiol-treated women (63). Young women with hypogonadotropic hypogonadism (HH) are probably a better model to see the effect of estrogen on female sexual function. Barut *et al.* performed a case-control study recruiting sexually active women with HH and aged 22–41 years; in the HH group, the levels of estrogen in the blood was below 50 pg/mL and 68% of patients reported SD – compared to only 30% in the control group. Furthermore, women with HH had lower scores on the FSFI than control subjects in all analyzed domains, thus showing a relationship between HH and SD, most likely

due to the effects of reduced levels of ovarian hormones. The bigger limitation of this study was the absence of data after therapy (64) (Table 5). Another paper (65) analyzed the sexual function in case of congenital hypogonadism (OCH) and Turner's syndrome (TS) without considering estrogen levels because all women were receiving hormone replacement therapy. No differences between TS subjects and the OCH group were found in FSFI domains, and patients with OCH scored lower with respect to the controls, but the poor sexual functioning may not be correlated with specific hormones.

While systemic (or at least local) estrogen administration remains the best treatment of female SD due to congenital, acquired, or age-dependent ovarian failures, such as genitourinary syndrome of menopause, many women, mostly in the latter group, do not accept the hormone replacement therapy (HRT) because of justified or unmotivated fear of neoplastic consequences (66). Genitourinary syndrome of menopause (GSM) describes the syndrome which is associated with estrogen decrease, and includes, 'but is not limited to, genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections' (citing the definition by Portman *et al.* (67)). Ospemifene is a new interesting selective estrogen receptor modulator (SERM) which binds to estrogen receptors and results in activation of the estrogenic pathways in some tissues (agonism, such as in vagina) and blockade of the same pathways in others (antagonism, such as in the breast). Hence, ospemifene has an estrogen agonist/antagonist activity which selectively makes vaginal tissue thicker and less fragile, resulting in a reduction in the amount of GSM-dependent pain women experience with sexual intercourse (68). Interestingly, patients treated with ospemifene have significantly greater adherence and persistence compared with the other local estrogen therapies (69). A recent meta-analysis of available controlled studies showed that the incidence of vaginal bleeding, endometrial cancer, breast tenderness, and breast and endometrial cancer was not

significantly different in ospemifene-treated patients with respect to general population (70). On the basis of all these findings, ospemifene appears as a new tool in the hands of the endocrinologist for the treatment of moderate to severe symptomatic GSM in post-menopausal women who are not candidates for systemic nor local vaginal estrogen therapies.

In conclusion, these data suggest that estrogens improve sexual function in young and old women; however, while many reports recommend the use of estrogen or ospemifene in GSM during menopause (71), few data are available for young women with estrogen deficiency.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is among the most frequently diagnosed endocrine affections in females of reproductive age and features polycystic ovarian morphology, ovulatory dysfunction, and metabolic abnormalities (72, 73). Most affected patients develop menstrual irregularities, such as oligomenorrhea, and hyperandrogenism: both these conditions can have a devastating psychological burden and possibly negatively impair sexual health and function (72). Six studies have investigated female sexual dysfunction in PCOS patients by using the FSFI; five studies (74, 75, 76, 77, 78) found no significant difference in all domains, whereas a single study (79) reported worse scores for arousal, lubrication, pain, and satisfaction in PCOS women. A systematic review and meta-analysis by Zhao *et al.* (80) which included the aforementioned studies, as well as others using different questionnaires, concluded that PCOS does not increase the risk of female SD, although lower scores for the arousal and lubrication domains were reported. These findings, however, require some caution: PCOS is a variable clinical entity, with symptoms ranging from mild to severe, which can also affect sexual development when occurring in adolescence by negatively influencing self-esteem. In adulthood, PCOS can lead to obesity,

Table 5 Sexual function domains (according to the Female Sexual Function Index (FSFI)) and endocrine diseases associated with female sexual dysfunctions.

Sexual desire	Hyperprolactinemia, hypoandrogenism, diabetes, and estrogen deficiency
Sexual arousal	Hyperprolactinemia, diabetes and hypercortisolism
Lubrication	Hypothyroidism, diabetes, and hypercortisolism
Orgasm	Diabetes and hypercortisolism
Satisfaction	Diabetes and hypercortisolism
Pain	Diabetes and estrogen deficiency

depression, and infertility, all of which can negatively affect sexual health (80). Even if current evidence does not suggest a substantial effect of PCOS on sexual health, investigating sexual functioning is suggested in order to identify and treat any subclinical SD before its eventual transition to overt dysfunction.

Testosterone deficiency

In women, testosterone deficiency is difficult to define as commercial testosterone radioimmunoassays have low accuracy. Even studies that validated the accuracy of RIA against a highly sensitive testosterone assay have limitations, as the precision of the assay was scarce at the lower end of the female range. In fact, a large, cross-sectional Australian study has demonstrated that no single androgen level is predictive of low female sexual function. In this study, androgens were measured with RIA (81). Recently, the association between androgens and sexual desire was investigated in 560 healthy Danish women 19 to 65 years old (82). In this study sex steroids were measured by liquid chromatography and sexual desire was measured by the FSFI. Both free testosterone and androstenedione were significantly associated with sexual desire in the entire group after adjustment for age. Free and total testosterone levels were associated with sexual desire in women 19 to 24 years old, and total and free testosterone, androstenedione, and DHEAS were associated with sexual desire in women 25 to 44 years old who were not using systemic hormonal contraception. In a previous study, Basson and colleagues did not find reduced androgen activity in women with hypoactive sexual desire, but they found significantly lower levels of the two precursor steroids DHEAS and androstenediol (83). They concluded that women receiving testosterone supplementation should be informed that an absolute androgen deficit has not been demonstrated in dysfunctional women.

Randolph *et al.* investigated the associations between sex steroids and follicle-stimulating hormone and self-reported sexual function in participants in the Study of Women's Health Across the Nation (SWAN) (84). Women were asked to report how often they felt desire and how frequently they engaged in masturbation in the previous 6 months. Testosterone was positively associated with frequency of masturbation and desire and the lower quartile of testosterone was negatively associated with frequency of masturbation, desire, and arousal. DHEAS was positively associated with frequency of masturbation and desire.

Taken together, all these studies demonstrate relations between androgen levels and sexual interest and arousal in women, but more studies are necessary to establish the cutoff level for androgen that will distinguish women with low desire from women with normal sexual function (81).

A new interesting avenue of research, which may provide interesting data for the endocrinologist treating female SD, is the transdermal and topical use of testosterone. A position statement issued in 2019 by several societies studying female sexual health, among which the International Menopause Society, the Endocrine Society, the International Society for Sexual Medicine, and the International Society of Endocrinology, clearly states that treatment of HSDD is the only evidence-based indication for testosterone therapy in post-menopausal women (85). The hormone was indeed approved as patches of 300 µg for the HSDD in women with precocious menopause (86). However, very few gynecologists and endocrinologists prescribed it and very few patients requested this treatment, despite the evidence that HSDD is a very frequent sexual symptom in menopause. This 'testosterone Waterloo' was due to several factors, such as the lack of medical interest in female sexual desire, the absence of specific culture in sexual medicine, the often irrational and not evidence-based public worry of hormones, and the mentioned difficulties in dosing low levels of testosterone in women (87). The local administration of androgens could be the future: some double-blind, placebo-controlled clinical trials have demonstrated that local vaginal DHEA may improve SD in post-menopause, such as moderate to severe dyspareunia (88). The rationale of the use of the weak androgen DHEA in the menopausal vagina is probably to be found in the *bona fide* androgen-dependence of the anatomical structures named clitoris-urethra-vaginal (CUV) complex, which is the trigger of sexual pleasure during the vaginal penetration (89). Moreover, having made clear that the clitoris itself, differently from the penis, maintains its full responsivity to testosterone at all ages of the woman (90), we are currently exploring the use of low doses of testosterone gel on the postmenopausal clitoris with preliminary encouraging results.

Diabetes

Diabetes is known to be one of the most diffuse non-communicable chronic diseases affecting sexual life (2); its complications, neurological, micro- and macro-vascular, endocrine, and psychiatric are potentially

debilitating and might severely impair the SQoL. In men, both vascular and neurological impairment ultimately affect erectile function (91); additionally, male SD is prominently featured in conditions such as the metabolic syndrome and diabetes in which the inflammatory status, atherosclerosis, and oxidative stress are associated with worsening erectile functioning (92). Despite the large body of evidence supporting a role for diabetes in male SD, female sexual function is not frequently considered in clinical trials investigating complications of diabetes. However, sexual function in both sexes is largely compromised in diabetes (93), as pioneering studies have demonstrated (94). In fact, recent meta-analysis studies investigating this topic have proven that female SD has high overall prevalence (95), being featured in all types of diabetes and significantly associated with depression (96). Meta-regression analysis has also suggested an increased prevalence of female SD over the last 15 years, possibly suggesting increased awareness concerning female sexuality in recent years (95).

Many factors are likely involved in the pathogenesis of SD in female diabetic patients. Salonia *et al.*, in 2006, proved that most domains of sexual function are compromised in type 1 diabetes, including arousal, lubrication, satisfaction, orgasm, and pain (97). More recently, Maseroli *et al.* have reviewed literature investigating the association between cardiovascular risk factors and female SD: endothelial dysfunction in the female genital tissues could provide a pathophysiological explanation for such association, although a direct cause-effect relationship cannot be taken for granted (98). Reduced blood flow to genital tissues can lead to impaired engorgement of clitoris and vagina, ultimately resulting in reduced peripheral arousal (99, 100); in a recent study on young women, Coppola *et al.* have correlated FSFI and clitoral tissue perfusion measured through transmucosal oxygen tension, proving that vascular dysfunctions at such level negatively affect arousal, lubrication, orgasm, and satisfaction (101), even after adjusting for age, BMI, and smoking. Additionally, Tuncel *et al.* have reported that all domains of the female sexual response are significantly impaired in type 2 diabetes: older age, longer duration of diabetes, insulin and antidepressant therapy, and presence of hypertension are also associated with worse sexual functioning (102), providing additional proof of the multifactorial involvement of diabetes in female SD. In these regards, the psychological consequences of diabetes should not be underestimated: quality of life is severely affected by diabetes and its complications (103), and among diabetic patients, depression is seemingly

more prevalent in females (104, 105, 106). Furthermore, depression in diabetic and pre-diabetic patients, measured via the Beck Depression Inventory scale, negatively correlates with the FSFI score (107, 108). Interestingly, metformin treatment aimed to improve glycemic control has also shown positive effects on the different domains of the FSFI, most notably on sexual desire and sexual satisfaction (109). We are currently evaluating if and how addressing SD in diabetic patients of both sexes may increase the compliance to challenging adjustments in the lifestyle and to difficult therapies, characteristics of this chronic and worsening disease.

Gout

Gout is a common metabolic disease resulting from accumulation of uric acid and its crystallization in the joints and tendons. Gout is associated with a significant impairment in QoL, mostly resulting from pain and disability (110); however, SQoL is also affected (111). Surprisingly, a single study has addressed the association between gout and sexual function in women, although without the use of the FSFI: the authors concluded that both the physical and the emotional components of intimacy were compromised by gout, with a significant burden on relationship in both men and women (112). Despite the small sample size and the lack of standardized inventories for assessment of sexual function, this study underlines that sexual health is an often-neglected aspect in gout patients.

Conclusion

In last few years, the numbers of studies that evaluated sexual function in women with endocrine diseases increased. Most of them were small placebo-controlled pilot studies, but their conclusions indicate that, frequently, sexual alterations are associated to endocrine diseases. Several mechanisms affecting sexual health have been identified, such as micro- and macro-vascular alterations in diabetes, impaired androgen action or secretion in adrenal diseases, and inhibitory effects on reproductive and sexual function through hyperprolactinemia. In most cases, the presence of an underlying condition – even a *minor* condition, such as in the case of autoimmune thyroid disease – seems to impair sexual function, possibly for psychological as well as organic reasons. Additionally, different domains of sexual health seem to be affected

by different conditions (Table 5). It is, therefore, often difficult to understand whether the sexual disorder is directly linked to hormonal alterations, partly because studies are small and partly because the causes of sexual pathologies are complex. Blindly prescribing blood tests is never suggested. Indeed, clinical judgment and suspicion should guide the diagnostic process, based on the signs and symptoms accompanying sexual dysfunction in affected patients. Future research should aim to identify the unexplained mechanisms through which several endocrine diseases can impair sexual function, as in the case of hyperthyroidism or GH deficiency. In some cases, hormonal therapy has led to an improvement in the sexual function, strengthening the hypothesis of a close correlation between hormonal alterations and sexual disorder. The endocrinologist should discuss with patients about their personal sexual function, using in the daily clinical practice old (113, 114) and new (115) well validated psychometric tools and offer them alternatives for evaluation and treatment if, as frequently occurs in female endocrine patients, an SD is present. It is also worth mentioning that sexual health is a fundamental part of QoL, and therefore, in all cases psychological and therapeutic support should be provided in order to guarantee a satisfying sexual function to all patients, no matter their age or the concomitant illnesses.

Declaration of interest

E A J is or has been consultant and/or paid speaker for the following companies: Bayer, Ibsa, Lundbeck, Menarini, Otsuka, and Pfizer. The other authors have nothing to disclose.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author contribution statement

E C and A S equally contributed to the intellectual content of this review article.

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Received 11 November 2019

Revised version received 10 February 2020

Accepted 1 April 2020