8 Female Sexual Dysfunctions: A Clinical Perspective on HSDD, FAD, PGAD, and FOD

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Abbreviations

CBT	Cognitive behavior therapy
cGMP	Cyclic guanosine monophosphate
CNS	Central nervous system
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DSDS	Decreased sexual desire screener
DSM	Diagnostic and Statistical Manual (of Mental Disorders)
FCAD	Female cognitive arousal disorder
FGAD	Female genital arousal disorder
fMRI	Functional magnetic resonance imaging
FOD	Female orgasm disorder
FOIS	Female orgasmic illness syndrome
FSD	Female sexual dysfunction
FSFI	Female Sexual Function Index
FSIAD	Female sexual interest/arousal disorder
GPPPD	Genito-pelvic pain/penetration disorder
GSM	Genitourinary syndrome of menopause
HMB	Heavy menstrual bleeding
HPF	Hyperactive pelvic floor
HSDD	Hypoactive sexual desire disorder
IBS	Irritable bowel syndrome
ICD	International Classification of Diseases and Statistics
IDA	Iron deficient anemia
ISSWSH	International Society for Women's Sexual Health
MCR	Melanocortin receptor
MRI	Magnetic resonance imaging
NO	Nitric oxide
PDOD	Pleasure dissociative orgasmic disorder
PF	Pelvic floor
PGAD	Persistent genital arousal disorder
PGAD/GPD	Persistent genital arousal disorder/genito-pelvic dysesthesia

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SFQ	Sexual Function Questionnaire
SHBG	Sex hormone-binding globulin
SNRIs	Serotonin and norepinephrine reuptake inhibitor
SSRIs	Selective serotonin reuptake inhibitors
STP	Sexual tipping point
UTI	Urinary tract infection
VAS	Visual analogue scale
VPA	Vaginal pulse amplitude
VPP	Vaginal photoplethysmography
VVA	Vulvovaginal atrophy
WHO	World Health Organization

8.1 Female Sexual Dysfunctions: A Clinical Perspective

8.1.1 Introduction

Sexual dysfunction encompasses a disturbance in sexual functioning involving one or more phases of the sexual response cycle, including pain associated with sexual activity. Classifications are still evolving; they are a real nosographic "work in progress." Historically, two classification systems have been used for sexual medicine diagnosis: the Diagnostic and Statistical Manual of Mental Disorders (DSM), edited by the American Psychiatric Association, and the International Classification of Diseases and Statistics (ICD), endorsed by the World Health Organization (WHO). In addition, throughout the past decades, sexual medicine experts from various international societies have been constantly working to revise and redefine the nomenclature of female sexual dysfunctions (FSDs), in order to reflect the updated scientific evidence and the ever-changing standards in clinical care for women with sexual problems [1]. Disease classification systems provide a standard and internationally comparable system for use in national and international information and reporting.

However, three major drawbacks persist. First, the aim of perfectly describing the elusive complexity and nuances of female sexual function and dysfunction leads to the usage of complicated definitions that are difficult to use with and be understood by colleagues not specifically trained in sexual medicine. Conversing with patients is even more challenging. Second, it is difficult to translate sophisticated definitions from English to national languages in easy-to-catch words that adhere to the human daily experience. Third, and most importantly, the persisting neglect or scotomization of prominent biological etiologies of FSD. This contributes to maintaining a wide gender bias, overfocusing on the psychodynamic/relational/contextual etiology of FSD.

Commonly accepted diagnostic criteria play a critical role in framing the interpretation of concepts in the medical and epidemiological literature, influencing how healthcare providers organize their thoughts about clinical conditions, how populations are defined in trials, and allowing global information exchange among clinicians, patients, and healthcare systems [1]. The classifications of FSDs followed over the years reflect the evolution of the female sexual response models. In the 1960s, Masters and Johnson published "Human Sexual Response," proposing the first model of the human sexual response cycle in both men and women, consisting of four stages: excitement/arousal, plateau, orgasm, and resolution. In 1979, Kaplan added the concept of desire to be applicable to a non-laboratory setting. Kaplan conceived sexual desire as an "appetitive phase" localized in the brain, initiating a cascade of physiological, genitally-focused events. Both these models are known as "linear," since they postulate that sexual response begins with spontaneous sexual desire and proceeds from one stage to the next; this framework became the basis for the conceptualization, classification, and definitions of FSDs in the DSM-IV [2] and DSM-IV-TR [3]. In the early 2000s, Basson introduced the circular incentive-based model of the female sexual response, suggesting that women may be motivated to engage in sexual activity for many sexual and non-sexual reasons, including wanting to enhance intimacy or bonding, to feel attractive or desired, or to communicate affection for a partner, and therefore may start a sexual experience in a state of "sexual neutrality" [4]. Women can also engage in sexual activity to gain personal and/or

economic advantages, starting in a non-aroused state. According to this alternative conceptualization, women may experience desire once sexual stimuli have triggered arousal (concept of "responsive desire"). Arousal and desire often co-occur and reinforce one another. These new concepts, along with several perceived shortcomings of previous models [5], led to suggestions that informed the DSM-V definitions [6].

It should be noted that crucial intra- and inter-individual differences exist in the physiological sexual response and that no single model is universal; however, among women, sexual dysfunction and distress have been reported to be significantly related to the endorsement of the Basson model [7].

8.2 Sexual Interest/Desire Disorders

8.2.1 Pathophysiology of Low Desire

In both sexes, the sexual desire construct underlies cognitive and emotional processes that are ultimately controlled by systems and neurotransmitters in the central nervous system (CNS) that modulate sexual excitation and inhibition. According to the "Sexual Tipping Point" (STP) model®, the continuous interplay between excitation and inhibition generates a dynamic, personal threshold for sexual responsiveness, which is subjected to variations at any given time in the individual [8]. The regions that modulate sexual desire in the CNS are located in the hypothalamus, limbic system, and prefrontal cortex, and include the medial preoptic area, paraventricular nucleus, ventral tegmental area, and nucleus *accumbens* [9]. Neural pathways controlled by dopamine, and secondarily by melanocortin, norepinephrine, and oxytocin, facilitate the processing and response to sexual stimuli [9]. In particular, dopaminergic neurotransmission positively regulates reward-related neural functions, including sexual reward [10]. In contrast, sexual inhibition is modulated by serotonin, opioid, and endocannabinoid systems that are activated during the refractory period and can blunt excitatory processes [9]. These conditions (or drugs) that influence neurotransmission in these key regions, resulting in decreased excitation, increased inhibition, or both, may predispose individuals to hypoactive sexual desire disorder (HSDD). Such dynamic alterations can be reinforced by negative sexual experiences, which can potentiate sexual inhibition.

Cumulative evidence from preclinical and clinical studies indicates that sex steroids act as major neurofunctional modulators of sexual desire in women. In mammalian and rodent females, the sexual motivation peak observed during the periovulatory period is probably driven by ovarian hormone actions, triggering central excitatory mechanisms [11]. Estrogenic priming has been reported to be necessary for progesterone-modulating effects on dopaminergic transmission [12]. In female rats, the lordosis reflex is dependent on estrogen, whereas the full expression of appetitive and consummatory behaviors depends on additional activation by progesterone [13].

Evidence that androgens are crucial determinants of women's sexual desire stems mainly from studies on postmenopausal women with HSDD treated with testosterone therapy (see Sect. 8.2.5). Although there is no threshold for any androgen that can be used to diagnose women with FSD, a recent meta-analysis concluded that there appears to be a moderate association between endogenous total testosterone levels and sexual desire [14]. Studies on female rats treated with estradiol, testosterone, and aromatase inhibitors first suggested that aromatization may not be necessary for testosterone to increase the sensitivity of the response to male-related cues [15]. These data were confirmed in subsequent experiments, in which the administration of the non-aromatizable androgen dihydrotestosterone (DHT) in estradiol-primed ovariectomized rats was able to enhance behavioral measures of sexual desire [16]. It is likely that the excitatory role of androgen signalling in the reward system in humans is implicated in such effects on sexual desire. However, sex hormones act among a myriad of other biological and psychological variables to shape sexual motivation.

8.2.2 Nosology and Current Definitions

In the DSM-V, the classical distinct definitions of desire and arousal problems were collapsed into a new entity called "female sexual interest/arousal disorder" (FSIAD) [6]. This revised classification has proven highly controversial among clinicians and experts, mainly because of the little empirical support for new diagnostic categories and the practical consequences on management, with many women with incomplete loss of receptivity likely to be excluded from any diagnosis [17]. Subsequent international panels, the International Consultation in Sexual Medicine [18], and the International Society for Women's Sexual Health (ISSWSH) Nomenclature Committee [19] restored the label of hypoactive sexual desire disorder (HSDD). Specifically, according to the nosology and nomenclature for FSDs recently proposed by ISSWSH, HSDD "manifests as any of the following for at least 6 months: (1) lack of motivation for sexual activity as manifested by decreased or absent spontaneous desire (sexual thoughts or fantasies), decreased or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity; (2) loss of desire to initiate or participate in sexual activity, including behavioral responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders and is combined with clinically significant personal distress that includes frustration, grief, incompetence, loss, sadness, sorrow, or worry" (grade B, level of evidence 2–3) [20]. Similarly, in the updated version of the ICD-11, HSDD is characterized by "[…] (1) reduced or absent spontaneous desire (sexual thoughts or fantasies), (2) reduced or absent responsive desire to erotic cues and stimulation, or (3) inability to sustain desire or interest in sexual activity once initiated […]" [21]. In both definitions, symptoms must be associated with clinically significant distress to constitute dysfunction.

8.2.3 Prevalence and Leading Etiologies of HSDD

HSDD in women is a multifactorial condition that includes biological, psychosexual, and contextual factors. The differences in the design of epidemiological studies assessing the prevalence of HSDD (concerning definitions, settings, and methodologies) have produced estimates ranging from 17% to over 50% [22]. Data from the PRESIDE study, a large population-based survey conducted on more than 50,000 US women, showed that low desire was the most common sexual difficulty, reported in 37.7% of participants, whereas low desire with associated distress (HSDD) was present in 10% of responders [23].

However, the exact biological alterations that determine HSDD have not yet been characterized. Clinically, no neuroimaging or biochemical parameters can identify women with HSDD. Aging is one of the main factors affecting sexual desire; however, the younger the woman, the higher the distress that this loss may cause. Menopause has a further worsening impact, and premature iatrogenic menopause is the most frequent cause of biologically determined generalized loss of desire [24]. This is probably due to the sudden decline in ovarian sex steroids, namely estrogens and androgens [25], since the ovaries contribute more than 50% of androgens during the reproductive life. In a cross-sectional survey of European women aged 20–70 years, surgical menopause was associated with a significantly and clinically relevant higher risk of HSDD than natural menopause and premenopausal status [26].

Several general medical conditions, including neurologic, oncologic, and metabolic disorders, may represent risk factors for HSDD. Indeed, chronic diseases interfere with sexual function through multiple mechanisms, including fatigue and the psychological burden of a lifelong progressive diagnosis [27]. Psychiatric disorders, such as depression, are also major determinants of low sexual desire and display a bidirectional

relationship, with depressive symptoms conferring a 50–70% increased risk of HSDD and HSDD being associated with a 130–210% increased risk of depression [22, 28]. Furthermore, a number of medications, i.e., psychotropics (antipsychotics, barbiturates, benzodiazepines, lithium, serotonin reuptake inhibitors, tricyclic antidepressants, and venlafaxine), cardiovascular and antihypertensive drugs, GnRH agonists and analogs, hormonal contraceptives, antiandrogens, tamoxifen, aromatase inhibitors, and chemotherapeutic agents, have been associated with desire disorders [29].

All pathological and physiological conditions that determine lower androgen and free androgen levels, besides iatrogenic menopause, may result in diminished desire [14]. Among these, pregnancy, puerperium, lactation, pathological hyperprolactinemia, hypopituitarism, hypothalamic amenorrhea, adrenal insufficiency, primary ovarian insufficiency, and increased sex hormone-binding globulin (SHBG), which is common in women using hormonal contraception, are particularly important [30].

Chronic sleep disorders, in terms of reduced quantity and/or poor quality of sleep, are major and still neglected contributors to HSDD through different pathways, with hyperactivation of the corticotrophin-releasing pathway, hypothalamic dysregulation, and increasing daily distress and fatigue [31].

Box 8.1 Iron Deficient Anemia (IDA): The Most Neglected Non-hormonal Biological Etiology of HSDD in Women

Key Points

- Iron deficiency anemia (IDA) is highly prevalent in women (30–50% in low-income countries) [32].
- IDA doubles the risk of depression, a major contributor to HSDD [33].
- Iron is essential for the synthesis of dopamine, the key neurotransmitter of the "seeking-appetitive lust system" [34].
- Leading etiologies of IDA in women include:
  - Low iron intake (poverty, eating disorders, vegan diet, "self-made diet," and aging).
  - Reduced intestinal absorption (celiac disease, lactose intolerance, gluten intolerance, irritable bowel syndrome (IBS), and Crohn's disease).
  - Increased losses:
    Menstruation: Heavy menstrual bleeding (HMB) occurs in 19–20% of women.
    Delivery with postpartum hemorrhagia.
    Oral-gastro-intestinal: gingivitis, gastritis, IBS, and hemorrhoids.
  - Increased needs:
    Adolescence
    Pregnancy
    Athletes
  - Reduced availability from storage sites, during chronic inflammatory diseases

Key Clinical Point. Careful clinical history-taking, with a few inexpensive examinations (red blood cell count, hemoglobin, serum iron, ferritin, and transferrin levels), is essential to address IDA, a key and still neglected etiology of HSDD.

The most vulnerable are women with HMB and women after delivery, if iron supplementation was inadequate during pregnancy and/or if delivery caused heavy blood loss.

Box 8.2 Sexual Pain: The Underappreciated Killer of Sex Drive

Feedbacks from the genitals are powerful modulators of sex drive:

- Positive sexual experiences, with fast systemic and genital arousal, intense gorgeous genital congestion (the "orgasmic platform," according to Master and Johnson), and intense orgasm(s) are

powerful enhancers that potentiate sexual desire and drive [35].

- Negative sexual experiences, specifically genital pain, may gradually inhibit any sex drive and sexual response. Vulvar pain, recurrent post-coital cystitis, introital and/or deep dyspareunia, vulvovaginal atrophy (VVA), and genitourinary syndrome of menopause (GSM) may all contribute to impaired sex drive, up to a frank aversion of any coital intimacy [36]. Previous sexual abuse can have a long-lasting impact on sex drive through multiple pathophysiological pathways, both biological and psychosexual [37].

Key Clinical Point. A thorough clinical history of comprehensive sexual pain disorders is essential for every woman complaining of HSDD. Every woman should also undergo a competent genital evaluation to diagnose and treat all the clinical conditions that could contribute to her complaints of HSDD. The hyperactive pelvic floor (HPF) should be carefully diagnosed and addressed, as it is a powerful yet neglected etiological contributor to FSDs. HPF can cause reduced genital arousal and lubrication due to pain, sexual pain disorders, genito-pelvic pain penetration disorders (GPPPD), recurrent post-coital cystitis, coital anorgasmia, and painful anal sex.

Psycho-relational factors play a key role in the etiology of HSDD. The most commonly reported are poor self-esteem/body image issues; lifestyle factors (e.g., stress and sleep deprivation); a history of abuse (physical, sexual, and emotional); substance abuse; self-imposed pressure for sex; religious, personal, cultural, or family values; beliefs and taboos; relational conflicts; and sexual factors (e.g., inadequate stimulation and sexual dysfunction in the partner) [22].

8.2.4 Diagnostic Algorithms and Tools

Conventionally, an accurate diagnosis of HSDD requires a time-consuming and extensive diagnostic interview performed by a clinician with expertise in FSD. The key aspects to address when assessing low desire are as follows: (a) whether the disorder is generalized (occurring with every partner and in every situation) or situational; in fact, situational problems often exclude medical factors; (b) the onset and duration, that is, whether the symptoms are lifelong or have been acquired after months/years of satisfying sexual function, and in this case, which are the factors that the woman feels contributes to or precipitates the symptoms; and (c) her level of distress and bother, which defines the mild, moderate, or severe impact of the dysfunction on her personal life [24].

It is crucial to distinguish sexual distress from nonsexual distress and depression. From a couple's perspective, a discrepancy in the level of desire between two partners is common and does not qualify the person with the lower desire to have HSDD per se. The patient should be diagnosed with HSDD only if the discrepancy causes her personal distress [22].

Although obtaining a detailed description of a woman's problem is important to establish the diagnosis and guide treatment, many women with HSDD are at risk of remaining undiagnosed because of limited access to experts trained in FSD. Screening tools play a pivotal role in this context. For example, the brief profile of female sexual function (B-PFSF) [38] and the decreased sexual desire screener (DSDS) [39] are both sensitive and easy-to-use brief diagnostic instruments that help identify HSDD in women who present with a complaint of decreased sexual desire.

The Female Sexual Function Index (FSFI) [40] is considered the gold standard for the measurement of sexual function in women and provides different scores for several sexual domains, including desire. In fact, the two-item desire domain is the only one that can be used independently, with women with scores of ≤ 5 being

likely to meet the diagnostic criteria for HSDD [41]. However, the FSFI does not examine distress, a key diagnostic component included in both the DSM and ICD diagnostic systems [42]. For this reason, it is recommended that a validated scale assessing distress be administered along with the FSFI desire domain when making clinical inferences, such as the female sexual distress scale—revised (FSDS-R) or the FSDS-R item 13, a specific question that addresses the level of distress related to low sexual desire [43].

8.2.5 Key Therapeutic Approaches

The ISSWSH process of care for the management of HSDD in women suggests that first-line therapeutic strategies are represented by sexual education and modification of potential biological and psychological contributing factors [22]. For example, sexual pain or arousal disorders should be addressed *before* a specific treatment for HSDD is considered, as relieving these symptoms may improve desire per se. In the case of generalized acquired HSDD persisting, the key therapeutic approaches include psychological sex therapy, testosterone treatment, and centrally acting drugs based on the menopausal status [22]. Due to the multifactorial origin of HSDD, it is crucial that its treatment is planned from a patient- and couple-centered, multidimensional perspective, sequencing options that target either the suspected primary contributing component or the more distressing component for that individual woman to that individual woman [44].

The most common psychological therapies are behavior therapy (i.e., sensate focus exercises), cognitive behavior therapy (CBT), and mindfulness-based CBT [45–47]. Although these are based on a strong rationale, there is a paucity of clinical trials and a lack of adequate control groups to clearly establish the efficacy of these interventions [44].

As physiological and pathological changes in androgen levels influence sexual function in women, they represent a potential target for therapeutic strategies for HSDD. Specifically, systemic transdermal testosterone has been recommended for women with HSDD not primarily related to modifiable factors or comorbidities [48]. A 1% (10 mg/mL) cream is currently approved in Australia, whereas this approach is currently off-label worldwide. A recent Global Position Statement, endorsed by several international societies, suggests that treatment should be administered to naturally or surgically postmenopausal women, with or without concurrent estrogen therapy, in doses that approximate physiological testosterone concentrations for reproductive age [49]. This was mainly based on a meta-analysis of randomized controlled trials supporting the moderate therapeutic benefit, increase in desire (standardized mean difference 0.36, 95% CI 0.22–0.50) and reduction in sexual caused by transdermal testosterone compared to the effects of placebo/comparator therapy [50]. No serious adverse events to testosterone therapy have emerged [50], although long-term safety has not yet been established. Owing to the lack of efficacy and safety data, compounded products should not be used, and government-approved transdermal male formulations may be prescribed cautiously in doses appropriate for women [49]. Expert opinion reports usually suggest one-tenth of the daily dose prescribed to men undergoing replacement therapy for hypogonadism (300-μg/24-h testosterone) [51]. Limited evidence supports the use of testosterone in premenopausal women of late reproductive age [48]. The key messages regarding testosterone treatment are summarized in Table 8.1.

Regarding other androgen-based options for HSDD, a meta-analysis conducted in 2014 showed that dehydroepiandrosterone (DHEA) administration did not significantly impact sexual symptoms in postmenopausal women with normal adrenal function [52].

The centrally acting drugs for HSDD are flibanserin and bremelanotide, which focus on the inhibitory and excitatory pathways linked to the regulation of sexual desire (see Sect. 8.2.1). Flibanserin is a 5-HT1A receptor agonist and 5-HT2A receptor antagonist that has been approved as an oral therapy (once daily, at bedtime) against acquired, generalized HSDD in premenopausal women in the United States (US),

Table 8.1 Key practical points for systemic testosterone therapy, off-label in most countries, according to the "International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women" [48]

Systemic testosterone therapy for women
Who: postmenopausal (natural or surgical) women with HSDD (± other FSDs), with or w/o estrogen replacement
When: after/during appropriate management of other conditions that may contribute to low desire
How: intramuscular injections and oral preparations are not recommended. Transdermal dosing should be targeted to achieve T concentrations in the physiologic premenopausal range
How long: on an average, efficacy emerges after 6–8 weeks; maximal at about 12 weeks. Discontinue after 6 months if no improvement; no safety data >24 months
Formulations: compounded products lack evidence for efficacy and safety. It is reasonable to prescribe off-label approved male formulation at approximately 1/10th of the male dose
T levels monitoring: no blood level as a treatment goal. Total T levels should be measured before initiating therapy to exclude women with midrange to high baseline concentrations, 3–6 weeks after initiating therapy and after 6 weeks if dosing is increased to exclude over-dosing; every 4–6 months once stable levels are achieved

HSDD hypoactive sexual desire disorder, *FSD* female sexual dysfunctions, *T* testosterone

and in naturally postmenopausal women aged 60 years or younger in Canada [53]. Bremelanotide is a melanocortin receptor (MCR) agonist administered via subcutaneous injection on demand before sexual activity. By binding to presynaptic MC4R, bremelanotide has been suggested to stimulate the release of dopamine in key brain regions and has been approved in the US for acquired, generalized HSDD in premenopausal women only [54]. Finally, an off-label CNS agent that has been reported to improve HSDD symptoms is bupropion, a dopamine, and serotonin reuptake inhibitor [55].

Sexual Interest/Desire Disorders: Key Points

- Low desire reflects a dynamic imbalance between excitatory and inhibitory central mechanisms, in favor of the latter.
- Hypoactive sexual desire disorder (HSDD) is characterized by a reduced or absent, spontaneous or responsive desire for several months, associated with clinically significant distress.
- HSDD is the most common form of female sexual dysfunction (10–50%).
- Risk factors for HSDD include the following:
  - Systemic conditions, such as aging, menopause (+ surgical), general medical diseases, pathologic, and physiologic (i.e., puerperium) conditions associated with the loss of fluctuations in ovarian hormones, depression and other psychiatric diseases, and medications (i.e., psychotropic drugs)
  - Negative feedbacks from the genitals such as vaginal dryness, sexual pain, vulvar pain, inadequate or absent orgasm, hyperactive pelvic floor, post-coital cystitis, and the genitourinary syndrome of the menopause (GSM)
  - Psycho-relational factors
- Screening tools: B-PFSF, DSDS, and FSFI-D + FSDS-R.
- First-line therapeutic strategies: Sexual education and modifications of contributing factors (i.e., sexual pain, hyperactive pelvic floor, loss of sexual hormones, and treatment of iron-deficient anemia).
- Second-line strategies: Psychological sex therapy (behavior therapy and CBT), testosterone treatment, and centrally acting drugs (flibanserin and bremelanotide).
- Short-term transdermal testosterone treatment in post-menopausal women with HSDD, aimed at restoring premenopausal levels, has proved to be safe and effective.

8.3 Arousal Disorders

8.3.1 Pathophysiology of Genital Arousal Disorders

"Arousal" refers to the physiologic responses that occur during an anticipatory period before and during sexual activity, up to the moment of climax. These encompass both cognitive/emotional and physical components, involving genital (swelling and vaginal lubrication) and non-genital manifestations (increased heart rate, sweating, and hardening of the nipples).

Genital arousal depends on the anatomical and functional integrity of the complex neural, endocrine, and vascular mechanisms, ultimately resulting in increased blood flow. This clinically translates into the engorgement of erectile tissue, such as the clitoral, vestibular, and periurethral corpora cavernosa (homologous to their penile counterpart), and the production of a fluid transudate in the vagina, known as "lubrication." Female genital tissues are rich in arterial vascularization, supplied by branches of the internal pudendal and femoral arteries (labia), ileo-hypogastric pudendal bed (clitoris), branches of the uterus (upper vagina), hypogastric arteries (middle vagina), and middle hemorrhoidal and clitoral arteries (distal vagina) [56]. Briefly, immediately after sexual stimulation, parasympathetic pathways (via the pelvic nerves) lead to the release of vasodilator neurotransmitters in the genital tissues, mainly nitric oxide (NO). NO induces the formation of cyclic guanosine monophosphate (cGMP), which in turn stimulates cGMP-dependent protein kinase (protein kinase G), leading to the relaxation of the vascular smooth muscle cells [57]. The subsequent increase in blood flow and pressure results in the formation of a plasma ultrafiltrate within the vaginal epithelial cells, accumulating at the vaginal surface as a clear, smooth fluid that moistens the vaginal walls, allowing painless penile penetration [56]. It is important to emphasize that it has never been demonstrated that glandular secretion in the human vagina determines its lubrication during arousal.

In the late 1990s, following pivotal experiments performed in female animal models of aortoiliac atherosclerosis, Park et al. theorized that an abnormal arterial circulation or endothelial function within the hypogastric-cavernosal vascular bed could interfere with physiologic arousal processes and manifest with diminished or delayed vaginal lubrication and sensation, pain or discomfort during intercourse, and diminished clitoral sensation or orgasm [58]. These hypotheses have been confirmed by subsequent studies in animal models [59] and humans [60], and observational data have suggested an association between cardiovascular risk factors (e.g., diabetes mellitus) and poor genital arousal [61]. However, adequate studies aimed at establishing a cause-and-effect relationship between FGAD and cardiovascular diseases in women have not been conducted, and currently, there are no conclusive data to support that FGAD is a predictor of future cardiovascular events [62].

Among the lifestyle-related factors, smoking and cycling may significantly impair genital arousal in women. In a laboratory study, acute nicotine use has been shown to reduce genital arousal by 30% in women [63]. Cigarette smoking, both active and passive, is the strongest modifiable predictor of FSD, including genital arousal disorders, in women [64]. Bicycle seat pressure on the perineum may impair arousal and clitoral erection, likely contributing to the genital pain and numbness experienced by female cyclists, similar to the genital and sexual symptoms affecting male cyclists. A survey of female cyclists indicated that 53.9%, 58.1%, and 69.1% of female cyclists had FSD, genital numbness, and genital pain, respectively. After adjusting for age, body mass index, relationship status, smoking history, comorbidities, and average time spent cycling per week, women who reported experiencing genital numbness half the time or more were more likely to have FSD (adjusted odds ratio [aOR], 6.0; 95% CI, 1.5–23.6; $P = 0.01$), especially if localized to the clitoris (aOR, 2.5; 95% CI, 1.2–5.5; $P = 0.02$) [65].

More genital numbness and urinary tract infections (UTIs) were confirmed in another, larger survey, which does not confirm the

increased arousal vulnerability reported in the former study. From a clinical point of view, it is important to ask women complaining of female sexual arousal disorder (FSAD) about leisure activities, bicycling particularly, and comorbid complaints of genital numbness, UTIs, and/or saddle sores [66].

8.3.2 Nosology and Current Definitions

The definitions of altered arousal have varied greatly over the years. The DSM-IV-TR identified "female sexual arousal disorder" (FSAD) focusing solely on the lack of an "adequate lubrication-swelling response to sexual excitement," [3] failing to mention non-vaginal responses. As previously reported in the DSM-V, arousal disorder was not described as a distinct diagnostic entity, but rather merged with HSDD, to create the combined diagnostic category of FSIAD (female sexual interest/arousal disorder) [6]. This combination was driven mainly by studies suggesting that FSAD and HSDD are often comorbid and that many women are unable to differentiate desire from arousal [5]. However, the cumulative evidence has not only shown that desire and arousal may be disconnected, but also that a dramatic between-person variability exists in the concordance between "subjective" (positive mental engagement during sexual activity) and "physiological arousal" (vaginal lubrication and other genitals and non-genitals sensations) [67]. In this context, a recent line of research has highlighted the notion that some women are mentally aroused by perceived genital cues, whereas for others, the two types of arousal are asynchronous [68]. These aspects may have clinical implications in the diagnosis and treatment of arousal disorders.

Ultimately, the updated and revised nomenclature proposed by the ISSWSH differentiates female genital arousal disorder (FGAD) from female cognitive arousal disorder (FCAD) [69]. FGAD is characterized by "the distressing difficulty or inability to attain or maintain adequate *genital response*, including vulvovaginal lubrication, engorgement of the genitalia, and sensitivity of the genitalia associated with sexual activity, for 6 months" (grade B) [69]. On the other hand, the diagnosis of FCAD is based on "the distressing difficulty or inability to attain or maintain adequate *mental excitement* associated with sexual activity as manifested by problems with feeling engaged or mentally turned on or sexually aroused for 6 months" (expert opinion) [69]. Both disorders may induce mild, moderate, or severe distress and may be experienced independently or in different combinations.

8.3.3 Prevalence and Leading Etiologies of Female Genital Arousal Disorder

The lack of a clear definition and standardized diagnostic tools has severely limited epidemiological studies on female sexual arousal disorders. In the PRESIDE study, previously mentioned regarding the prevalence of low desire, the overall, unadjusted prevalence of low sexual arousal (without distress), and low sexual arousal inducing distress were 26.1% and 5.4%, respectively. The age bracket displaying the highest prevalence of 7.5% was the middle-aged group (45–64 years) [23]. No data are available on the prevalence of FGAD and FCAD according to the most recent nomenclature.

The current definition of FGAD underlines the importance of organic insults which disrupt the neurovascular mechanism underpinning the genital response to sexual stimuli; in fact, it has been reported that the etiology of FGAD is related to vascular and neurologic injury or dysfunction [69]. Among cardiometabolic diseases potentially causing FSD, diabetes mellitus is probably the one showing the strongest correlations; the more heavily impaired sexual domains in diabetic women are arousal and lubrication [70]. Some studies have indicated that age, duration of disease, metabolic control, and microangiopathic complications, in particular, neuropathy [71], are independently associated with sexual difficulties in women with diabetes [61]. Based on limited evidence, obesity, meta-

bolic syndrome, dyslipidemia, and hypertension may also increase the risk of vasculogenic FSD; however, this effect appears milder than that in men [62].

Regarding neurological integrity, arousal difficulties are common in women with disorders affecting both the central and peripheral nervous systems. Sexual symptoms are often underdiagnosed in patients with spinal cord injury or multiple sclerosis [72]. Pudendal neuropathy (i.e., following childbirth) and radiculopathy of the sacral spinal nerve roots due to sacral or lumbar spinal pathologies, such as disc impingement or spinal stenosis, can also result in genital arousal disorders [73]. Pelvic irradiation and surgery (i.e., hysterectomy or pelvic organ prolapse surgery) are other commonly neglected causes of possible damage to small blood vessels and nerve endings in genital tissues [74]. Interestingly, vaginal delivery has been associated with significantly decreased scores in the sexual arousal domain of the FSFI [75].

A hyperactive pelvic floor, lifelong, or acquired in response to inflammation and/or pain, which reduces the vaginal opening and causes pain during penetration attempts, may cause reflex inhibition of both mental and genital arousal, contributing to poor or absent lubrication [73].

Furthermore, estrogens and androgens seem to play a synergistic role as regulators of the contractile-relaxant machinery underlying peripheral arousal, both in the vagina [76] and in the clitoris [77]. Therefore, low sex steroids levels may contribute to poor vaginal lubrication and clitoral tumescence. However, concerning the effect of estrogen and androgen deficiency, vulvovaginal atrophy, and/or the genitourinary syndrome of menopause (GSM), along with vulvovaginal infections and inflammatory disorders, are considered as *exclusion criteria* for FGAD [69]. However, the exclusion of leading biological etiologies of impaired genital arousal, such as the post-menopausal loss of sexual hormones, deprives women of a very simple and appropriate treatment for vaginal dryness, dyspareunia, and/or other comorbid symptoms of GSM. Since biological/organic etiological factors such as diabetes or radiotherapeutic damage are considered, GSM and the associated loss of sex hormones should also be considered.

In addition, modifiable lifestyle-related factors, such as smoking or bicycling, that could contribute to the onset and maintenance of genital arousal disorders in women should be actively investigated and appropriately treated.

Finally, psycho-relational factors are believed to affect both cognitive and genital arousals. Depression, anxiety, body image concerns, eating disorders, environmental stressors, cultural attitudes, history of sexual abuse, poor sexual stimulation, low relationship satisfaction, communication issues, and sexual dysfunction in the partner (in particular, male premature or delayed ejaculation) should always be evaluated in women complaining of arousal difficulties [78].

The interdependence between the different phases of the sexual response is almost the rule in clinical practice. Different biological etiologies may contribute to different FSDs. To create rigid boundaries, defining a specific disorder more clearly may become a boomerang in clinical practice if the relevant predisposing, precipitating, or maintaining factors of genital arousal impairment are excluded.

8.3.4 Diagnostic Tools for Arousal Disorders

One of the major flaws in the study of female arousal is the lack of a universal, objective, and feasible approach aimed at diagnosing a state of impaired genital blood flow, unlike in men. Penile color Doppler ultrasound performed in non-stimulated conditions is considered the gold standard for the investigation of erectile dysfunction of suspected vascular origin and is commonly performed in clinical practice [79]. Most importantly, assessing the hemodynamic parameters of the penile arteries can provide important information on cardiovascular risk, especially in young and low-risk men [79]. A homologous technique in women has not yet been validated, and the vast majority of data on alterations of female genital arousal have been based on self-

report measures, a methodology flawed by a great susceptibility to response bias.

In laboratory settings, the most well-established method for measuring genital blood flow is vaginal photoplethysmography (VPP), which uses a device that emits and reabsorbs light. The rationale of this method is that the amount of backscattered light depends on the transparency of the vaginal tissue, reflecting its variable vasocongestion [80]. The provided measure, known as the vaginal pulse amplitude (VPA), has been found to be a sensitive and reliable marker of genital sexual arousal.

Clitoral artery Doppler ultrasound has been proposed as a noninvasive and objective approach to measuring genital blood flow and is easier to use in clinical settings compared to VPP [81, 82]. However, this technique has not been fully validated, and the most reproducible hemodynamic parameters (peak systolic velocity, resistance index, pulsatility index, and volume flow) and their normative values have yet to be established. Other methods include indirect measures of heat dissipation (i.e., vaginal and labial thermistors and heated oxygen electrodes), thermal imaging cameras, and laser Doppler perfusion imaging [80]. Finally, Schirmer tear test strips have recently been suggested as an objective measure of vaginal lubrication [83].

Arousal-related items in the common female sexual health questionnaires are as follows: Brief Index of Sexual Functioning (BISF-W): 5,13,14; Sexual Function Questionnaire (SFQ): 7,8,9,10,11,12,13,14; female arousal and desire inventory (FADI) (all items); Sexual Interest and Desire Inventory (SIDI): 11,12; Female Sexual Function Index (FSFI): 3,4,5,6 [78].

8.3.5 Key Therapeutic Approaches

The primary strategy to alleviate FGAD symptoms is to address modifiable causes such as poor vascularization due to atherosclerosis and neuropathy due to sacral and lumbar pathologies. In clinical practice, topical sexual hormones (when not contraindicated) are very effective in improving both vascular and neurogenic responses, in addition to addressing the mucosal component of FGAD. The reported subjective improvement correlates well with the objective trophism improvement at the vulvovaginal examination and the lowering of the vaginal pH from 7 to 4.00–4.5 in postmenopausal women complaining of FGAD. Women should be informed that this is an off-label treatment option. The clinical results reported by women are more satisfactory when a co-present hyperactive pelvic floor, lifelong or defensively acquired because of FGAD, is treated with appropriate physiotherapy.

According to the literature, in the absence of drugs with this specific indication, women with FGAD may benefit from vaginal moisturizers and lubricants as a symptomatic approach. In fact, a minimalistic, although in-label approach, plays a role when even topical hormones are contraindicated or not desired by the individual woman. Moisturizers are intended to be used regularly and act by rehydrating mucosal tissue and trapping moisture. On the other hand, lubricants are based on water, silicone, minerals, or plant oil, and are applied as needed to reduce friction during sexual activity. When considering these products, the ideal parameters are body-similar pH (3.5–5) and osmolality (200–600 mOsmol/kg), and a lack of parabens, chlorhexidine, and polyquaternium-15, to reduce the risk of endothelial irritation and side effects [84].

Vibrators, devices that combine vibration and clitoral vacuum suction, and other mechanical devices may provide useful treatment options [85]. Those containing phthalates, polyvinyl chloride, vinyl, and jelly rubber should be avoided.

The most widely studied topical vasodilating agent in women is alprostadil, a synthetic form of prostaglandin E1 that can induce genital smooth muscle relaxation by increasing protein kinase A activity. It has been reported that alprostadil increases genital temperature, arousal [86], and clitoral peak systolic velocity [87] with no significant adverse events. Several promising data are also available for visnadine, a principle extracted from the plant *Ammi Visnaga,* capable of inhibiting smooth muscle contractile responses mediated by calcium entry. A 1% visnadine vulvar spray seems to improve sexual performance

in women with arousal disorders [88]. Regarding systemic vasodilators, the evidence is less convincing, with meta-analytic data showing an overall improvement in sexual function compared to that with a placebo, but with some studies have reported negative findings [89]. Significantly higher rates of headache, flushing, and changes in vision have emerged in phosphodiesterase type 5 inhibitor (PDE5i)-treated patients than in those treated with placebos [89].

Women suffering from FGAD associated with vulvovaginal atrophy (VVA) and/or GSM are candidates for the use of approved local estrogen treatments and DHEA. Local prasterone (DHEA) is indicated for moderate-to-severe VVA in postmenopausal women and has been consistently reported to improve several sexual domains, including arousal [90]. The efficacy of local DHEA, a precursor of both estrogen and androgens, appears to be mediated by the activation of androgenic signaling within the vaginal smooth muscle layer [91]. Systemic testosterone treatment in menopausal women with HSDD [49] and intravaginal testosterone [92] have also been reported to enhance arousal measures; however, both are considered off-label.

A comprehensive biopsychosocial treatment plan is advisable to provide women with the most holistic approach to ameliorate FGAD/FCAD. Psychological management options include sensate focus therapy, cognitive behavioral therapy, and mindfulness therapy [78].

Arousal Disorders: Key Points

- Female genital arousal disorder (FGAD) is characterized by the distressing, persistent impairment in the genital sexual response, including vulvovaginal lubrication and engorgement of the genitalia. The prevalence is around 5–10%.
- Female cognitive arousal disorder (FCAD) is a recently proposed diagnostic category characterized by the distressing, persistent impairment in mental excitement during sexual activity.
- Genital arousal depends on the anatomical and functional integrity of neural and vascular mechanisms, resulting in increased blood flow.
- Risk factors for FGAD include all those conditions causing vascular/endothelial and neurologic injury or dysfunction in the genitals, such as cardiometabolic risk factors (i.e., diabetes mellitus), spinal cord injuries, multiple sclerosis, pudendal neuropathy, sacral radiculopathy, pelvic irradiation, or surgery. Low sex steroids levels may contribute to damaging the integrity of small vessels and nerves.
- There is a lack of standardized, reliable, easy-to-use methods to assess genital arousal. Vaginal photoplethysmography (VPP) and clitoral Doppler ultrasound are two of the most studied. Other proposed tools include indirect measures of heat dissipation, thermal imaging cameras, laser Doppler perfusion imaging, and Schirmer tear test strips.
- Therapeutic strategies: No government-approved drugs are available. After addressing modifiable causes, women with FGAD may benefit from vaginal moisturizers and lubricants, vibrators, or topical vasodilating agents (i.e., alprostadil and visnadine). When vulvovaginal atrophy is also present, symptoms may improve with approved (local estrogens and prasterone) or off-label treatments (local or systemic testosterone).
- Sensate focus therapy, cognitive behavioral therapy, and mindfulness therapy are useful for FGAD/FCAD.

8.4 Persistent Genital Arousal Disorder/Genito-Pelvic Dysesthesia

The existence of persistent genital arousal disorder (PGAD) was first postulated in the early 2000s, but systematic characterization has only recently been attempted.

Persistent genital arousal disorder/genito-pelvic dysesthesia (PGAD/GPD) is currently defined as the "persistent or recurrent, unwanted or intrusive, distressing sensations of genital arousal [that occur over a] duration of at least 3 months" [93]. Other types of genito-pelvic dysesthesia (buzzing, tingling, burning, twitching, itching, and pain) may be described. PGAD/GPD is most commonly experienced in the clitoris but may also involve other genito-pelvic regions; the sensations may include being on the verge of an orgasm, experiencing uncontrollable orgasms, and/or having an excessive number of orgasms. The estimated prevalence is approximately 0.6–3% [93]. It is noteworthy that PGAD/GPD is not associated with concomitant sexual desire or fantasies and should not be misdiagnosed as hypersexuality. In fact, it has been reported to have a dramatically detrimental impact on the patient's sexuality, relationships, mental health, and daily functioning [94].

The underlying pathological mechanism has not been clarified; sensory hyperactivity originating in the genitals, pelvic/perineum, cauda equina, spinal cord, or brain has been theorized. Recognized organic risk factors for PGAD/GPD include clitoral, vestibular, vulvar, and vaginal pathology (i.e., vulvodynia, infectious and inflammatory conditions), overactive pelvic floor (PF) dysfunction, pudendal neuropathy, perineal vascular pathology (i.e., pelvic varices or arteriovenous malformations), sacral Tarlov cysts, and lumbar disc disease (i.e., annular tears); CNS organic disorders (i.e., epilepsy); and medications (trazodone, use of or discontinuation of SSRIs/SNRIs) [93].

PGAD/GPD treatment is guided by the identification of the eventual "trigger region," which may be performed through Doppler ultrasound of the clitoral cavernosal artery, local anesthesia testing, neurological testing, electromyography, transperineal ultrasound of the PF muscles, or diagnostic pudendal nerve blocks. If radiculopathy of the lumbosacral nerve roots is suspected, specific neurogenital testing is recommended, with targeted diagnostic injections of local anesthetic at the level suggested by magnetic resonance imaging (MRI) [93].

Psychosocial associated and contributing factors should be addressed, such as anxiety and depressive symptoms, suicidality, obsessive-compulsive symptoms, catastrophization, sexual or emotional trauma, psychiatric comorbidities, sexual functioning, and relationship adjustment [94].

In patients with symptomatic Tarlov cysts or lumbar disc disease, neurosurgical interventions have been reported to be beneficial in the vast majority of cases [95, 96]. Promising results have been obtained by neurolysis of the dorsal nerve to the clitoris, relieving compression of the pudendal nerve [97]. Psychotherapy, sacral/pudendal neuromodulation, and electroconvulsive therapy are other treatment strategies. Off-label pharmacological agents aimed at symptom control may also be considered (anticonvulsants, GABAergic activators, opioid inhibitors of neurotransmission, and SSRI/SNRI) [93].

8.5 Orgasm Disorders

8.5.1 Pathophysiology of Orgasm

Orgasm in women has been defined as "a variable, transient peak sensation of intense pleasure, creating an altered state of consciousness" and inducing a state of "well-being and contentment" [35]. Orgasm may be accompanied by involuntary, rhythmic contractions of the pelvic floor musculature, and uterine and anal contractions [35]. This phenomenon displays wide interpersonal variability in terms of the intensity, duration, and type of required stimulation. In a recent multicenter study conducted on young women in a monogamous stable heterosexual relationship, the stopwatch-measured time to orgasm was approximately 13 min [98]. Although the exis-

tence of differently activated organs in women is still debated, evidence suggests many possible triggers: mental, from imagery alone, nipple/breast stimulation, clitoral, vaginal, cervical, anal, etc. [99]. In recent decades, it has been recognized that the vagina and cervix are not insensitive, passive organs, but have a unique and significant sensory cognitive representation, and their stimulation is able to elicit orgasmic sensations [100]. In clinical practice, many women report experiencing orgasm with clitoral stimulation, while others report vaginal penetration, or both. This has been correlated with the anatomical variability of the human clitoris-urethrovaginal complex [99].

Genital sexual stimuli reach the spinal cord mainly in the lumbosacral segments via the pudendal (clitoris), pelvic, and hypogastric nerves (vagina), and are transmitted to supraspinal sites via the spinothalamic and spinoreticular systems; ascending inputs then activate neurons in several areas of the CNS. Recent functional magnetic resonance imaging (fMRI) studies have suggested that, during female orgasm, the activated brain regions include sensory, motor, reward, frontal cortical, and brainstem regions (e.g., nucleus accumbens, insula, anterior cingulate cortex, orbitofrontal cortex, hippocampus, amygdala, hypothalamus, and ventral tegmental area) [101]. The efferent arm of the spinal reflexes is involved in sympathetic, parasympathetic, and somatic activities. Moreover, during orgasm, the concentration of hormones and neurotransmitters related to bonding, such as prolactin and oxytocin, increases.

Multiple mechanisms may be correlated with alterations in orgasmic ability in women. Impairment of the central or peripheral afferent and efferent neural pathways involved in the regulation of the orgasmic response determines orgasmic failure [102]. For example, a spinal cord injury at S2-S4 would blunt the ability to perceive clitoral stimulation, since the pudendal nerves, which convey clitoral sensation, enter the spinal cord at this level.

The pelvic floor seems to play an important role in female orgasmic response. It has been demonstrated that pelvic floor muscles strength, evaluated using perineometer and surface electromyography, is positively correlated with self-reported orgasm ability in healthy volunteers [103]. Overactivity of the PF muscles may impair orgasm by preventing local tissue perfusion and compression of the clitoral, perineal, or rectal branches of the pudendal nerve [104].

Physiological orgasmic responses also depend on the balance between excitatory and inhibitory neurotransmitters in the brain [9], which may be disrupted by medications, drugs, or endocrine alterations (hyperprolactinemia, hypoestrogenism, and hypoandrogenism).

Finally, orgasmic capacity is deeply influenced by psychological and relational factors. Concerning autoerotism, orgasmic difficulty has been associated with young age, low masturbation frequency, low sexual relationship satisfaction, and masturbation practiced "to decrease sexual tension" or "to overcome anxiety" [105]. In another study, lesbian women reported more frequent orgasms than heterosexual women, and women who orgasmed more frequently reported receiving more oral sex, having sex for longer, being more satisfied with their relationships, talking about their sexual fantasies with their partners, and expressing love during sex [106]. Sexual inhibition has been found to act as an independent vulnerability factor for orgasmic difficulties in a large community sample [107]. In partnered sex, variance in orgasmic pleasure was mostly related to partner issues, sexual inhibition, lack of interest, and insufficient experience [108].

8.5.2 Nosology and Current Definitions

The definition of female orgasm disorder (FOD) in the DSM-IV-R was a "persistent or recurrent delay in or absence of orgasm after a normal sexual excitement phase" [3], that evolved in the subsequent edition to a "marked delay in, marked infrequency of, or absence of orgasm and […] marked reduced intensity of orgasmic sensations," inducing personal distress [6]. The most recent nomenclature proposal has broadened the

diagnostic criteria and included the concept of orgasm occurring "too early," as in the male counterpart, and of "orgasm without pleasure." Indeed, the ISSWSH defines FOD as a condition "characterized by a persistent or recurrent, distressing compromise of orgasm frequency, intensity, timing, and/or pleasure associated with sexual activity for a minimum of 6 months" [20].

Specifiers are related to the following: (a) frequency: orgasm occurs with decreased frequency (decreased frequency of orgasm) or is absent (anorgasmia); (b) intensity: orgasm occurs with decreased intensity (muted orgasm); (c) timing: orgasm occurs too late (delayed orgasm) or too early (spontaneous or premature orgasm) than desired by the woman; and (d) pleasure: orgasm occurs with absent or decreased pleasure (anhedonic orgasm or pleasure dissociative orgasmic disorder, PDOD) [20]. Traditional specifiers apply (lifelong vs. situational and generalized vs. situational).

In addition to the new entity PDOD, another provisional diagnosis based on expert opinion has been introduced: female orgasmic illness syndrome (FOIS). This condition is characterized by "peripheral and/or central aversive symptoms that occur before, during, or after orgasm, not related, per se, to a compromise of orgasm quality" [20]. Interestingly, confusion, decreased verbal memory, depression, seizures, and headaches have been reported among these bothersome sensations, as well as gastrointestinal symptoms, muscle aches, and fatigue.

8.5.3 Prevalence and Leading Etiologies of FOD

Orgasmic difficulties are also common. In a random sample of more than 1500 women from the US, 24% reported an inability to achieve orgasm for months in the previous year [109]. The prevalence of DSM-based FOD diagnoses, including distress, is approximately 5% [23].

Neurogenic FOD can be a consequence of CNS lesions, spinal cord injury, diabetic neuropathy, pudendal neuropathy, radiculopathy of the sacral spinal nerve roots due to herniation/compression by intervertebral discs, or other conditions. In women with multiple sclerosis, anorgasmia or hyporgasmia has been reported in up to 37.1% of cases [110].

Psychotropic medications, specifically mood stabilizers, antipsychotics, and antidepressants, often cause delayed or pleasure-less orgasm as a side effect, even after discontinuation [111]. A full history of medication use should be obtained in women with FOD.

A disordered function of the PF muscles that determines either increased activity (hypertonicity), diminished activity (hypotonicity), or inappropriate coordination may be associated with orgasm difficulties [112].

Vascular alterations in the genital bed and related risk factors (diabetes mellitus, obesity, smoking, and peripheral vascular disease) have been correlated with FOD because of the critical role of genital blood flow in peripheral sexual response [62]. Similarly, hormonal alterations that are known to undermine the anatomical and functional integrity of the genital tissue, especially low levels of androgens and estrogens, are potentially correlated with low sexual responsiveness and FOD. Furthermore, all inflammatory, infectious, and immunological conditions that determine dyspareunia (See Chap. 25) can indirectly affect the orgasmic function.

Pathological orgasm may also be experienced in the context of psychosocial issues. Poor body and genital image issues, negative emotions associated with sex, cultural background, shame or embarrassment due to religious beliefs, or familial inhibitions can contribute to anorgasmia or delayed orgasm [113]. Relationship issues should always be addressed; the lack of proper communication with the partner has been described as a key factor in women's orgasmic experience, as well as the partner's sexual dysfunction, such as premature ejaculation or erectile dysfunction [114].

8.5.4 Diagnostic Tools for Orgasm Disorders

Diagnosis requires complete pharmacological, psychosocial, and relational assessment. Genital physical examination is mandatory to assess the sensitivity and integrity of the structures involved.

Vulvoscopy, Q-tip testing, and smear testing are useful for identifying dermatological, inflammatory, and infectious conditions that may interfere with the peripheral sexual response. Laboratory testing is aimed at identifying women with low androgen levels, low estradiol levels, elevated prolactin, or dysthyroidism, who may benefit from replacement treatments or require further diagnostic workup to exclude endocrine diseases contributing to FOD.

In cases of specific clinical suspicion (i.e., vascular or neurological pathology), additional testing is advised. This may include pelvic floor physical therapy assessment, neurophysiological tests (i.e., evoked potentials of the pudendal nerve), MRI of the spine, clitoral/vulvar Doppler ultrasonography, or thermography.

The most commonly used psychometric measures for the evaluation of the subjective experience of the orgasm are the Orgasm Rating Scale [115] and the Orgasm domain of the Female Sexual Function Index [40]. A visual analog scale (VAS) named Orgasmometer-F has been validated in women to assess perceived orgasmic intensity [116]. Other recently developed tools include the Orgasm Beliefs Inventory [117] and the Bodily Sensations of Orgasm questionnaire [118].

8.5.5 Key Therapeutic Approaches

The modification of any reversible risk factors for FOD is recommended prior to considering any symptomatic intervention for desire and orgasm problems. The literature on symptomatic therapies for FOD is limited and contradictory, and there are no government-approved pharmacological treatments for this indication.

Specific randomized controlled trials on the effect of testosterone therapy on the orgasm domain of sexual function have not yet been published. However, a recent meta-analysis showed that compared to a placebo or comparator, testosterone significantly increased orgasms (SMD 0.25, 95% CI 0.18–0.32) in postmenopausal women [50]. Therefore, systemic testosterone treatment, which is off-label in most countries, may be an option for improving FOD in postmenopausal patients with comorbid HSDD.

Off-label agents including flibanserin and bremelanotide (both approved for HSDD in premenopausal women) and the antidepressant bupropion act on the balance of excitatory/inhibitory neurotransmitters, thus potentially facilitating the orgasmic response [119]. Vasodilating agents, such as sildenafil, have been suggested to improve orgasm measures in premenopausal women affected by sexual arousal disorder [120], whereas a less clear effect has been found in estrogenized postmenopausal women [121]; these data need to be confirmed.

Medical devices that provide vibratory stimulation or cause clitoral vascular engorgement by a vacuum system, ultimately enhancing arousal and orgasm, have been proposed as treatment approaches for FOD [122].

Compared with sexual pain disorders, very few studies have addressed the effect of physical therapy (i.e., Kegel exercises) on orgasm [123]. Therefore, conclusive evidence for a specific beneficial effect of FOD cannot be drawn. However, it has been suggested that in patients with hyperactivity of the PF muscles, a reduction in tone may improve orgasmic function [104]. In the clinical setting, appropriate relaxation training of the pelvic floor muscles in synergy with diaphragmatic breathing facilitates genital arousal, with improved genital congestion and lubrication, and can facilitate a more rapid and intense orgasm.

Psychological and behavioral treatments for FOD with the most consistent data include directed masturbation, sensate focus, and psychotherapy [124]. For example, directed masturbation is a cognitive-behavioral and mindfulness-based technique centered on stepwise exposure to genital stimulation. Available studies have demonstrated the efficacy of this type of therapy in FOD [124]. Other proposed approaches with little evidence include sex education, systematic desensitization, bibliotherapy, and coital alignment technique training; however, they may represent beneficial adjuncts [124].

Orgasm Disorders: Key Points

- Female Orgasm Disorder (FOD) is characterized by "a persistent or recurrent, distressing compromise of orgasm frequency, intensity, timing, and/or pleasure associated with sexual activity for a minimum of 6 months."
- Other recently proposed conditions relative to orgasm alterations are the pleasure dissociative orgasmic disorder (PDOD) and the female orgasmic illness syndrome (FOIS).
- The prevalence of orgasmic dysfunction including distress is around 5%.
- Leading etiologies of FOD are as follows: neurogenic conditions (secondary to CNS lesions, spinal cord injury, diabetic neuropathy, pudendal neuropathy, and radiculopathy of the sacral spinal nerve roots); use of medications disrupting the excitation/inhibition balance (i.e., mood stabilizers, antipsychotics, and antidepressants); pelvic floor muscles dysfunction (i.e., hyperactivity); vascular alterations in the genital bed and related risk factors (diabetes mellitus, obesity, smoking, and peripheral vascular disease); hormonal alterations (hypoestrogenism, hypoandrogenism, and hyperprolactinemia); psychosocial issues (sexual inhibition, poor body image, shame, or embarrassment due to cultural background); and poor communication with the partner or partner's sexual dysfunction.
- Diagnostic tools: pharmacological, psychosocial, and relational assessment; genital physical examination; and laboratory testing. Clinically-driven additional investigations include pelvic floor strength assessment; neurophysiological tests; MRI of the spine; and clitoral/vulvar Doppler ultrasonography or thermography.
- Psychometric questionnaires: Orgasm Rating Scale, Orgasm Domain of the Female Sexual Function Index, Orgasmometer-F, Orgasm Beliefs Inventory, and Bodily Sensations of Orgasm questionnaire.
- First-line treatment strategy: modification of any reversible risk factors. Off-label pharmacological therapies: systemic testosterone treatment in postmenopausal patients with comorbid HSDD, flibanserin and bremelanotide in premenopausal patients with comorbid HSDD, or bupropion; vasodilating agents. Medical devices (i.e., vibrators or vacuum systems) and pelvic floor physical therapy may be considered.
- Psychological and behavioral treatments for FOD with the most consistent data on efficacy are: directed masturbation, sensate focus, and psychotherapy.

8.6 Conclusion

The conceptualization, classification, and definition of FSDs are highly dynamic. The complexity of definitions is aimed at describing in the most comprehensive way the many differences and nuances of FSDs in different women and clusters of women. The purpose was to share definitions to standardize the frames and goals of research and investigations.

However, definitions are often difficult to translate into wording that is easy to use with colleagues who are not trained in sexual medicine and, even more importantly, with patients. The difficulty is greater when English definitions must be translated into other languages.

Therefore, the challenge is to find the optimal wording, matching the most comprehensive definition with words that are easier to understand, and best fitting the daily experience of women with sexual disorders. However, this challenge remains to be addressed.

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