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Etiology, diagnostic algorithms and prognosis of Female Sexual Dysfunctions

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Abstract

Objective: The aim of this paper is to review the etiology, diagnosis and prognosis of Female Sexual Dysfunctions (FSD), so as to increase the physician's competence in the evaluation of women's intimacy-related issues, sexual concerns and dysfunctions, with a special focus on biological etiology and the clinical examination.

Method: The etiology, diagnostic approach and prognosis of each sexual dysfunction is indicated via a literature review of the most relevant publications in this field.

Results: FSD's etiology is multifactorial. The most important causes include biological, psychosexual and contextual factors. When assessing FSD, the clinical history should assess if: a) the disorder is generalized or situational; b) the disorder is lifelong or acquired after months or years of satisfying sexual intercourse; c) the level of distress is mild, moderate, or severe in terms of the impact of the FSD on the personal life; and, d) the leading etiologies. To diagnose a sexual dysfunction, it is crucial to ask specifically about sexual function and avoid a collusion of silence that is all too common. A structured clinical history, selected examinations, and a very accurate physical examination are fundamental for a correct diagnosis.

Conclusions: Whatever the medical or genital sexual symptom complained of, a structured multidisciplinary, integrative approach is fundamental to the evaluation of the complex etiology of FSD.

Key words: Female sexual dysfunction, hypoactive sexual desire disorder, arousal disorder, orgasmic disorder, sexual pain disorder, dyspareunia, vaginismus, diagnosis, etiology, prognosis.

Introduction

Gynecologists are increasingly required to competently address women's sexual disorders. However most of them feel uneasy to open the Pandora's vase of female sexual disorders (FSD's) [1], with two major concerns: a) lack of specific training in this area; b) fear of "wasting their time" in lengthy histories and complicated dynamics during the clinical examination.

The goal of this paper is to distill the experience of the FSD European team group on the etiology, diagnosis and prognosis of FSD, to increase the physician's competence in the first line approach to women's intimacy-related issues, sexual concerns and dysfunctions. To ease the learning for a practical approach to FSD in the office, key aspects of the etiology and diagnosis of FSD will be commented with the gynecologist' perspective, with a special focus on the biological etiology and the clinical examination.

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The components of women's sexuality

Three major dimensions (female sexual identity, sexual function and sexual relationship) interact to give to women's sexual health its full meaning or its problematic profile [2-4]. Women's sexuality is discontinuous throughout the life cycle and is dependent on biological (reproductive events) as well as personal, current contextual and relationship variables. Gynecologists are therefore the physicians who naturally know more about: a) the impact of different reproductive endocrine changes on women's well-being, mood, and physiology of sexual response in the life span; b) the context related factors, rooted in family life, work-related issues and context-related causes of distress that may contribute to impair the sexual response. Trusting their existing knowledge is the first excellent starting point to increase the confidence and competence on sexual issues.

Co-morbidity between FSD and medical conditions (urological, gynecological, proctological, metabolic, cardiovascular and neurological disorders, besides the side-effects of pharmacological, surgical and/or radiotherapeutic treatments) is beginning to be recognized. The clinical scenario the gynecologist has built up across years of knowledge of his/her patients may therefore be the perfect base for a specific diagnosis when FSD's are disrupting the woman's and couple's quality of life.

Etiology of FSD

Definition and classification of FSD have been discussed in Mimoun and Wylie' paper, this issue. Some aspects of the etiology may overlap when considering different FSD, as they are interdependent in physiological and pathological dynamics. They will be mentioned again when their role is essential in the diagnostic scenario.

FSD's etiology is indeed multifactorial. Most important causes include:

- **biological factors:** hormonal dysfunctions, pelvic floor disorders, cardiovascular problems, neurological conditions (particularly pain related), metabolic disorders (diabetes), affective disorders (depression and anxiety). All the medical conditions that may directly or indirectly affect sexuality, through their multisystemic impact and/or iatrogenic factors [5, 6], i.e. the consequences of the pharmacologic, surgical and/or radiotherapy treatment, should be considered in the differential diagnosis of potential contributors to the reported FSD. Specifically, loss of sexual hormones, consequent to natural or iatrogenic menopause, is a major contributor to FSD [7]. This is the area where the gynecologist feels more confident are where his/her diagnostic accuracy may prove critical for the appropriate understanding of the disorder and pertinent treatment;
- **psychosexual factors:** they refer to emotional/affective/psychic factors such as negative upbringing-losses-trauma (physical, sexual, emotional) [8], body image issues [9], sexual aversion disorder (extreme anxiety and/or disgust at the anticipation of/or attempt to have any sexual activity) [10], binge eating disorders affecting self-esteem and self-confidence, attachment dynamics (secure, avoidant, anxious) that may also modulate the level of trust in the relationship, the intensity of the commitment, the confidence in loving and attitude towards affective and erotic intimacy, including the disrupting impact of partner's affairs. Unfortunately, this is an area usually neglected in the medical setting. Just recognizing the existence of these contributors should induce the gynecologist to refer the woman to the pertinent colleague;
- **contextual descriptors:** past and current significant relationships [11], current interpersonal difficulties, partner's general health issues and/or sexual dysfunctions, inadequate stimulation and unsatisfactory sexual and emotional contexts may contribute to FSD. Diagnosing partner-related issues, and specifically Male Sexual Disorders (MSD), that may induce, precipitate or contribute to maintain FSD, should induce the gynecologist to refer the partner to the uroandrogologist for a parallel diagnostic investigation and treatment.

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Hypoactive sexual desire disorder

Loss of desire is multifactorial. It includes biological, psychosexual and context-related factors [12]. Aging is the first factor affecting sexual desire in women [13] and menopause has a further worsening effect. Surgical menopause, secondary to bilateral ovariectomy, has a specific damaging effect due to the loss of ovarian estrogens and androgens. Ovaries contribute more than 50% of total body androgens in the fertile period of life. A European survey in 1356 women indicated that women with surgical menopause had an odds ratio (OR) of 1.4 [95% confidence interval (CI), 1.1 to 1.9; P=0.02] of having low desire compared with normal women. Surgically menopausal women were more likely to have HSDD than premenopausal or naturally menopausal women (OR=2.1; 95% CI=1.4 to 3.4; P=0.001). Women with HSDD were more likely to be dissatisfied with their sex life and their partner relationship than women with normal desire (p<0.001) [14]. Premature iatrogenic menopause is the most frequent cause of a biologically determined generalized loss of desire; the younger the woman, the higher the distress this loss may cause to her [3, 14].

Leading biological etiologies of HSDD include not only hormonal factors (low testosterone, low estrogens, high prolactin, or hypothyroidism), but also psychiatric disorders like depression and/or comorbidity with major diseases. Asthenia and fatigue, contributing to the loss of vital energy that deprives desire of its most powerful fuel, are the most complained symptoms during chronic diseases and the most neglected ones [15]. HSDD is also associated with the use of some medications, such as selective serotonin reuptake inhibitors (SSRIs), anti-hormones, anti-hypertensive agents, chemotherapy drugs, treatments of chronic diseases, and the misuse of alcohol and recreational drugs (opiates). Psychological causes, relationship and intrapersonal issues, or socio-cultural causes (poverty/low income, distressing or difficult working conditions or sexual norms) may be involved. These causes can be secondary to or co-morbid with any other sexual disorder (self or partner). There may be an overlap and an interaction between all of these factors.

Arousal disorder

One of the leading biological etiologies of arousal disorders is the loss of sexual hormones, primarily estrogen, as experienced in hypothalamic amenorrhea, postpartum amenorrhea during lactation, and menopause, in the absence of hormone therapy. Hormonal contraception is one specific cause of genital arousal disorder that is in the domain of the gynecologist and can cause the complaint of vaginal dryness, more frequently reported with the lowest level of estrogens [16]. A recent Australian study indicate that low genital arousal was more likely among women who were perimenopausal (OR 4.4, 95%CI 1.2-15.7), postmenopausal (OR 5.3, 95%CI 1.6-17.7), or depressed (OR 2.5, 95%CI 1.1-5.3), and was less likely in women taking hormone therapy (OR 0.2, 95%CI 0.04-0.7), more educated (OR 0.5, 95%CI 0.3-0.96), in their 30s (OR 0.2, 95%CI 0.1-0.7) or 40s (OR 0.2, 95%CI 0.1-0.7), or placed greater importance on sex (OR 0.2, 95%CI 0.05-0.5) [17]. Pelvic floor disorders also contribute to arousal disorders. Specifically, hyperactivity of the pelvic floor may reduce the introital opening causing dyspareunia. Pain is the strongest reflex inhibitor of genital arousal; genital arousal disorders, and the consequent vaginal dryness, are often co-morbid with dyspareunia [18]. Psychosexual and relational factors may also concur in this disorder. A hypoactive or damaged pelvic floor (after traumatic deliveries, with macrosomic children or vacuum or forceps extraction) may contribute to genital arousal disorder because it reduces the pleasurable sensations the woman (and the partner) feel during intercourse [19]. Also, diabetes and vascular factors [20] smoking, lower urinary tract symptoms (LUTS), pelvic surgery, neurological diseases, drugs as anti-hormones or chemotherapy, psychological and socio-cultural causes may be involved.

Orgasmic disorders

Causes may be biological (e.g., aging, pelvic floor disorder, modification of the pelvic floor after vaginal delivery or pelvic surgery, negative effects of neurological diseases, poor outcomes of genital mutilation), iatrogenic (e.g., medication with

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SSRI and other antidepressants), psychological or socio-cultural.

Sexual pain disorders

Dyspareunia is the common symptom of a variety of coital pain-causing disorders (Box 1). The most frequent etiology is biological. Pain perception can be worsened by psychological or contextual conditions [21]. Psychological and socio-cultural causes include intrapersonal issues, inadequate foreplay, inexperience, sexual norms, lack of erotic skills, and culturally based genital modifications (mutilation).

Vulvar vestibulitis is the leading cause of dyspareunia in women during the fertile stage of life. However it may be complained of after the menopause, during hormonal replacement therapy if *Candida* vaginitis (re)triggers introital pain. The diagnostic triad is: 1) severe pain upon vestibular touch or attempted vaginal entry; 2) exquisite tenderness to cotton-swab palpation of the introital area (mostly at 5 and 7, when looking at the introitus as a clock face); 3) dyspareunia. Vulvar lichen sclerosus is a major contributor of introital dyspareunia in the postmenopausal years.

Vaginismus is a painful spasm of pelvic floor muscles (levator ani) around the vagina. When mild, it makes intercourse painful, thus contributing to introital dyspareunia. Microabrasions secondary to the intercourse in dry conditions and with a tightened levator ani, may contribute to a chronic vestibular inflammation and vulvar vestibulitis. When severe, it makes intercourse impossible: vaginismus is the most common female cause of unconsummated marriage. It may be a local muscular expression of a systemic muscular tension, secondary to a general systemic arousal due to the phobic attitude. Alternately, it may be the expression of a local myogenic hyperactivity of the levator ani, isolated or secondary to genital, bladder, or anal pain [22].

Comorbidity with other sexual dysfunctions (loss of libido, arousal disorders, orgasmic difficulties, or sexual pain related disorders) is commonly reported with persistent or chronic dyspareunia.

Comorbidity between dyspareunia and other medical conditions is also frequent and under-reported. For example, in the survey of Peters and coworkers, interstitial cystitis was associated with a significantly higher incidence of dyspareunia and fear of intercourse since the first intercourse, suggesting that the hyperactivity of the pelvic floor and sexual pain disorders are important contributors to the pathophysiology of bladder chronic inflammation and pain [23].

Diagnostic approach to FSD

How to diagnose the patient with FSD? First of all the physician should always ask a few simple questions about sexuality, such as: "Are you currently sexually active?", and, if yes, "Are you satisfied or is there any concern or problem in your sexuality you'd like to raise and discuss?" This overture is precious to avoid the collusion of silence: otherwise, she may be too shy to disclose and the physician too busy to ask.

Based on the multifactorial etiologies, key aspects when assessing FSD include asking if:

- a) the disorder is generalized (with every partner and in every situation) or situational, specifically precipitated by personal, partner related or contextual factors, which should be specified [24]. Situational problems usually rule out medical factors that tend to affect the sexual response with a more generalized effect [19];
- b) the disorder is lifelong (from the very first sexual experience) or acquired after months or years of satisfying sexual intercourses. To ask the woman what in her opinion is causing the current FSD may offer useful insights into the etiology of the disorder, particularly when it is acquired [5];
- c) the level of distress that indicates a mild, moderate, or severe impact of the FSD on personal life [25]. Sexual distress should be distinguished from non-sexual distress and from depression. The degree of reported distress may have implications for the woman's motivation for therapy and for prognosis.

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Hypoactive sexual desire disorder

A screening tool to allow a postmenopausal woman to determine whether to seek evaluation for HSDD is the Brief Profile of Female Sexual Function (B-PFSF) that was developed using items from the Profile of Female Sexual Function (PFSF) [26, 27] and the Personal Distress Scale (PDS) [28]. This instrument is composed by seven questions, is easy to use in the office, and was found to provide good discrimination between postmenopausal women with HSDD and controls and to be a reliable and valid tool (Table 1) [29]. When questionnaire(s) are not used, the simplest disclosure and request for help are: "I have no more sexual desire" or "I've lost my desire and I'm sorry for my partner" or "I do not care anymore about sex, I have no interest in it at all, but my husband insists that I should consult a physician...".

Arousal disorder

When a patient complains of an arousal disorder, the clinician should first check if the disorder is mental ("I do not feel mentally excited"); genital ("I have vaginal dryness"; "It takes ages to get lubricated /wet") or mixed ("I do not get excited") [30]. The clinical history should investigate biological factors, psychosexual factors and affective states and context dependent/ relational factors as above.

Orgasmic disorders

Postmenopausal women may complain of two leading problems: "I did never have an orgasm, and would like to address this problem now before it is too late" (lifelong generalized anorgasmia) or, and more frequently, "My orgasm is now difficult to reach, it is weak, brief, no more satisfactory as it used to be, in spite of adequate foreplay and excitement" (acquired orgasmic disorder), or "I cannot have an orgasm any more" (acquired anorgasmia).

Sexual pain disorders

Those disorders can be easily reported because pain is in the traditional domain of the medical consultation. "We have sex rarely now, because I feel pain and my husband does not want to hurt me" or "I cannot have sex anymore because it hurts", or "Since I lost my periods, having sex has become more and more difficult. I have pain and sometimes cystitis afterwards. What should I do to regain a normal sex life?" These questions should immediately alert the gynecologist on a potential biological cause of the present complaint.

The clinical history should investigate:

- a) biological factors: besides the above mentioned strictly medical, the attention should be briefly focused on potential iatrogenic factors such as drugs [6] (antiandrogens; aromatase inhibitors; tamoxifen; hyperprolactinemic drugs such as sulpiride); and addictions (drugs, alcohol, smoke) [31];
- b) psychosexual factors and affective states, depression first of all, given the frequent comorbidity with desire disorders, with referral to a psychiatrist, a sex therapist or couples therapist for a comprehensive diagnosis and treatment if indicated. However, gynecologists are well aware that menopause may be associated with mood changes up to major depression and should evaluate and treat the potential endocrine contributor before referral. Evidence suggests that the response to antidepressant is potentiated by hormonal treatment in the postmenopause and may therefore contribute to both a more rapid improvement of depression and associated desire disorders [32, 33];
- c) context dependent/relational factors, including couple dynamics, or substantial factors such as work-aholism, professional distress, poverty. Partner's sexual or general health problems, contributing to a secondary loss of desire (in this case the partner is the "problem inducer" and the woman the "partner carrier") should be specifically

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investigated and, if present, appropriate referral considered. [34, 35]. However, FSD, and specifically sexual dissatisfaction, disinterest and even dysfunction, may be an appropriate response to an "antisexual" context (for example, a partner affected by male sexual disorders or abusive) [36] and they should not be labeled per se as "diseases" or dysfunctions requiring medical treatment. This is the reason why asking about the quality of the relationship is a key part of the clinical history to appropriately understand the sexual complaint.

Biochemistry should be included when the clinical history suggests a potential role of hormone changes/loss. The patient's hormonal profile should be investigated: total and free testosterone, dehydroepiandrosterone sulphate (DHEAS), prolactin, 17 β -estradiol, sex hormone binding globulin (SHBG), with a plasma sample on the third or fourth day from the beginning of the menses in fertile women when an hormonal contributor of either HSDD and/or arousal disorders is plausible. Follicle-stimulating hormone (FSH) and all of the above should be assessed in perimenopausal women, particularly when a premature menopause is considered. If individually indicated, thyroid-stimulating hormone (TSH) should be included. Appropriate investigation include glycemia and glycated Hb, when diabetes is suspected and/or when inadequate glycemic control and related metabolic syndrome may contribute to fatigue, depression and FSD [37, 38].

The glycemia, glycated hemoglobin and lipid profile may be indicated, particularly in smokers and/or hypertensive patients, as the different etiologies of cardiovascular diseases may contribute to vaginal dryness and impaired clitoral congestion. However, the evidence is solid in animal [39], while for women only preliminary data suggest a specific effect of the metabolic syndrome [40] and related disease as a contributor of vaginal dryness and clitoral hyporesponsivity.

The clinical examination is a mandatory, and still neglected, part of the assessment of women complaining of FSD, to evaluate potential genital factors that could contribute to erode the physical and motivational component of sex drive because of genitally rooted sexual dysfunctions. Specifically, the gynecologist should evaluate:

- a) the vulvar and vaginal trophism, as contributor of different FSD (acquired clitoral hyporesponsivity, associated with the genital aging, vaginal dryness, introital dyspareunia, orgasmic difficulties and acquired loss of desire); specifically, as mentioned, vulvar lichen sclerosus may contribute to introital dyspareunia;
- b) genital inflammatory conditions, such as vulvar vestibulitis, characterized by spontaneous or provoked acute pain at five and seven, if the introitus is considered like a clock face, introital dyspareunia and variable reddening of the introital mucosa. This disorder is more frequent in the fertile age but may be present during hormonal replacement therapy, as estrogens may trigger a recurrence of vaginal Candida and precipitate introital pain and vulvar vestibulitis;
- c) the pelvic floor, in all its components, with an accurate gynecological, sexological and/or psychiatric examination, particularly when an arousal, orgasmic and/or sexual pain disorders is reported. Attention should be paid to diagnose: i) hyperactivity of the pelvic floor, contributing to introital dyspareunia and post-coital cystitis. Typical signs at examination include: retracted perineum; "inverted command" (when the woman is required to push and she involuntarily pulls); localized pain ("tender point") when the examining finger presses the muscle at mid vagina, at the insertion on the ischiatic spine; or when the same maneuver elicits acute pain, irradiating toward the pelvis or the vulva ("trigger point"). In this case a "myalgic" pelvic floor can be diagnosed, as an isolated finding contributing to introital dyspareunia or as part of a more complex systemic disorder ("fibromyalgia"); ii) hypoactivity of the pelvic floor, which may be associated with coital hyposensitivity, coital anorgasmia, incontinence during thrusting;
- d) the vaginal pH, with a simple stick as vaginal acidity well correlates with estrogenic tissue levels and the vaginal ecosystem [19];

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e) poor outcomes of genital surgery (such as episiotomy-episiorrhaphy; posterior colporrhaphy; radical surgery for cervical cancer); or outcomes of vaginal, bladder or anal radiotherapy, leading to scarring, anatomic damage, with a short, retracted vagina, pain and secondary loss of desire [6];
f) signs of sexually transmitted diseases and/or poor outcomes of their treatment, such as in HPV related disorders [41];
g) traumatic consequences of female genital mutilation (infibulations);
h) signs and symptoms of urge, stress or mixed incontinence, associated with a hypertonic pelvic floor, the former, and a hypotonic pelvic floor, the latter [42]. Specifically, patients with clinical diagnosis of overactive bladder-dry had the highest sexual function while those with mixed urinary incontinence had the worst. Additionally, women with urinary incontinence (UI) and detrusor overactivity (DO) had the greatest degree of FSD, which was significantly worse than those with normal urodynamics. Additionally, for women with or without UI, the presence of DO on urodynamics resulted in a trend toward worse sexual function [43].

With a competent, multifactorial diagnosis, a multimodal treatment has the highest probability of improving the sexual complaint.

Based on all the factors described above, simple diagnostic algorithms are proposed for each female sexual dysfunction (Figures 1 to 4, source FSDeducation.eu) [see *Maturitas final article*].

Diagnostic tools

Diagnosis and treatment of female sexual dysfunction are currently based on subjective female reports and physical examination. Questionnaires such as the Female Sexual Function Index [44], the Profile of Female Sexual Function [26, 27] and the Personal Distress Scale [28], or more recent ones, such as the decreased sexual desire screener (DSDS) [45] are the most frequently tools used in the office setting. Specific instrument (such as vaginal probes to measure vaginal blood flow, or genitosensory analysis) are still in the research domain [46].

Prognosis

The prognosis of HSDD and arousal disorder is excellent, when an isolated endocrine factor is present, such as loss of testosterone after bilateral oophorectomy; is less favorable, when psychological and/or couple-related factors are associated with biological ones; is vulnerable to negative outcomes when lifelong psychosexual issues, couple related dysfunctions with complex unconscious dynamics and or serious organic disease impair the multisystemic basis of desire on both the biological and motivational side.

The prognosis of orgasmic disorders is excellent, when it is lifelong and due to erotic illiteracy, in couples erotically naïve; or, if acquired, when an isolated endocrine factor is present, such as loss of testosterone after bilateral oophorectomy, or when it is iatrogenic after treatment with SSRI; is less favorable, when psychological and/or couple-related factors are associated with biological ones and/or when the delivery associated disruption of the pelvic floor pubococcygeal fibers affects the muscular component of orgasm; is vulnerable to negative outcomes when lifelong psychosexual issues, couple related dysfunctions with complex unconscious dynamics and/or serious organic diseases (such as multiple sclerosis or other neurological diseases) impair the multisystemic basis of orgasm on both the biological and motivational side.

The prognosis of pain disorders is good when pain is acquired and associated with or secondary to vaginal dryness. It may be less favorable when dyspareunia is life-long, or associated with severe lichen sclerosus, chronic vulvodynia, pudendal neuropathy, genital mutilation, poor outcomes of posterior colporrhaphy, scarring of radical genital surgery and/or genital radiotherapy. It is vulnerable to negative outcomes when multiple biological etiologies are in play. Life-

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long vaginismus is easier to be cured when the patient is erotically naïve, even if already postmenopausal; it may be difficult to be treated if the myogenic component of the disorder is prominent.

Conclusion

Gynecologists and family physicians are the practitioners who can more easily integrate the FSD diagnosis in the body of their existing knowledge, just adding a few specific competences to the well structured scenario of pathophysiologic reading of women's endocrine, metabolic, and genital health. Whatever the medical or genital sexual symptom complained of, a structured multidisciplinary integrative approach is key to competently address the complexity of the etiology of FSD.

The first step is to take a careful clinical history. However, the specific diagnostic contribution of physicians in FSD is rooted in their accurate pathophysiologic reading, inspiring a structured clinical history, selected exams, and a very accurate physical examination, focusing on the usually neglected signs of vulvar dystrophy (or lichen), vaginal dystrophy/vaginal dryness, hyper/hypoactivity of the pelvic floor, iatrogenic negative outcomes of surgery and radiotherapy, negative outcomes of genital mutilation and urogenital comorbidity.

On a final note, the specific attention to the *wording* of FSD that will increase with increasing confidence and competence may further lead to a comprehensive diagnosis and appropriate treatment of the physical and emotional comorbidity of sexual disorders in women.

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