International Journal of Impotence Research (2005) 17, S44–S51
 0955-9930/05 $30.00
www.nature.com/ijir

Physiology of female sexual function and dysfunction

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Female sexual dysfunction is age-related, progressive, and highly prevalent, affecting 30–50% of American women. While there are emotional and relational elements to female sexual function and response, female sexual dysfunction can occur secondary to medical problems and have an organic basis. This paper addresses anatomy and physiology of normal female sexual function as well as the pathophysiology of female sexual dysfunction. Although the female sexual response is inherently difficult to evaluate in the clinical setting, a variety of instruments have been developed for assessing subjective measures of sexual arousal and function. Objective measurements used in conjunction with the subjective assessment help diagnose potential physiologic/organic abnormalities. Therapeutic options for the treatment of female sexual dysfunction, including hormonal, and pharmacological, are also addressed.
International Journal of Impotence Research (2005) **17,** S44–S51. doi:10.1038/sj.ijir.3901428

Keywords: female sexual dysfunction; anatomy; physiology; pathophysiology; evaluation; treatment

Incidence of female sexual dysfunction

Female sexual dysfunction is a multicausal and multidimensional medical problem that has both biological and psychosocial components. It is age-related, progressive, and highly prevalent affecting 30–50% of American women.[1,2] Based on the National Health and Social Life Survey of 1749 women, 43% have complaints of sexual dysfunction.[1] Recent studies evaluating the impact of age and estrogen status on the female sexual response demonstrated that older women and menopausal women not receiving hormone replacement therapy had decreased genital blood flow compared to controls.[3]

Ongoing epidemiological studies in women suggest that the same disease processes and risk factors that are associated with male erectile dysfunction including aging, hypertension, cigarette smoking, hypercholesterolemia, as well as pelvic surgeries are also associated with female sexual dysfunction.[4] Until recently, little basic science research or clinical has focused on female sexuality. One major barrier to the development of research in this field has been the absence of well-defined diagnostic classification system. The 1998 AFUD consensus Conference updated the definitions and classifications based upon current research and clinical practice. The definitions were broadened to include both psychogenic and organically based dysfunctions.[4]

The female sexual response cycle

Masters and Johnson[5] first characterized the female sexual response in 1966 as consisting of four successive phases: excitement, plateau, orgasmic, and resolution phases. During sexual arousal, both the clitoris and the labia minora become engorged with blood and vaginal and clitoral length and diameter both increase. Masters and Johnson observed that the labia minora increase in diameter by two to three times during sexual excitement and consequently become everted, exposing their inner surface. In 1979, Kaplan proposed the aspect of 'desire', and the three-phase model, consisting of desire, arousal, and orgasm, with desire being the factor inciting the overall response cycle.[6] This three-phase model is the basis for the DSM IV definitions of female sexual dysfunction, as well as the recent re-classification system made by the American Foundation of Urologic Disease (AFUD) Consensus Panel in October of 1998.[4] Others have recently suggested that sexual function should be considered as a circuit, with four main domains: libido, arousal, orgasm, and satisfaction. Each aspect may overlap and/or negatively or positively feedback on the next.[7]

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AFUD classification and definition of female sexual disorders

The Sexual Function Health Council of the American Foundation convened the AFUD Consensus Panel, an interdisciplinary consensus conference panel, consisting of 19 experts in female sexual dysfunction selected from five countries. The panel included specialists for endocrinology, family medicine, gynecology, nursing, pharmacology, physiology, psychiatry, psychology, rehabilitation medicine, and urology. The objective of the panel was to evaluate and revise existing definitions and classifications of female sexual dysfunction. Specifically, medical risk factors and etiologies for female sexual dysfunction were incorporated with the pre-exciting psychologically based definitions 1998 AFUD Consensus Panel Classifications and Definitions of Female Sexual Dysfunction.

Hypoactive Sexual Desire Disorder

The persistent or recurring deficiency (or absence) of sexual fantasies/thoughts, and/or receptivity to sexual activity that causes personal distress. Hypoactive Sexual Desire Disorder may result from psychological/emotional factors or be secondary to physiologic problems such as hormone deficiencies and medical or surgical interventions. Any disruption of the female hormonal milieu caused by natural menopause, surgically or medically induced menopause, or endocrine disorders, can result in inhibited sexual desire.

Sexual Aversion Disorder

The persistent or recurring deficiency (or absence) of sexual fantasies/thoughts, and/or receptivity to sexual activity, that causes personal distress.

Sexual Aversion Disorder is generally a psychologically or emotionally based problem that can result for a variety of reasons such as physical or sexual abuse, or childhood trauma.

Sexual Arousal Disorder

The persistent or recurring inability to attain, or maintain, adequate sexual excitement causing personal distress. It may be experienced as lack of subjective excitement or lack of genital (lubrication/swelling) or other somatic responses.

Disorders of arousal include, but are not limited to, lack of or diminished vaginal lubrication, decreased clitoral and labial sensation, decreased clitoral and labial engorgement or lack of vaginal smooth muscle relaxation. These conditions may occur secondary to psychological factors; however, often there is a medical/physiologic basis such as diminished vaginal/clitoral blood flow, prior pelvic trauma, pelvic surgery, or medications.

Orgasmic Disorder

The persistent of recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation and arousal that causes personal distress. This may be a primary (never achieved orgasm) or secondary condition, as a result of surgery, trauma, or hormone deficiencies. Primary anorgasmia can be secondary to emotional trauma or sexual abuse; however, medical/physical factors as well as medications (ie Seratonin re-uptake inhibitors) can contribute to or exacerbate the problem.

Sexual Pain Disorders

Dyspareunia: recurrent or persistent genital pain associated with sexual intercourse. Dyspareunia can develop secondary to medical problems such as vestibulitis, vaginal atrophy, or vaginal infection. It can be either physiologically or psychologically based, or a combination of the two.

Vaginismus: recurrent or persistent involuntary spasms of the musculature of the outer third of the vagina that interferes with vaginal penetration, and which causes personal distress. Vaginismus usually develops as a conditioned response to painful penetration, or secondary to psychological/emotional factors.

Other sexual pain disorders: recurrent of persistent genital pain induced by noncoital sexual stimulation. This includes anatomic and inflammatory conditions including infections (ie HSV), vestibulitis, prior genital mutilation or trauma and endometriosis.

These classifications are subtyped as lifelong *versus* acquired, generalized *versus* situational, and organic *versus* psychogenic or mixed. The etiology of any of these disorders may be multifactorial and often times the disorders overlap.

Physiologic changes in the vagina during sexual arousal

During sexual arousal, genital vasocongestion occurs as a result of increased blood flow. The vaginal canal is lubricated by secretions from uterine glands

and from a transudate that originates from the subepithelial vascular bed, passively transported through the intraepithelial spaces, sometimes referred to as intercellular channels. Engorgement of the vaginal wall raises pressure inside the capillaries and creates an increase in transudation of plasma through the vaginal epithelium.[8] This vaginal lubricative plasma flows through the epithelium onto the surface of the vagina, initially forming sweat-like droplets that coalesce to form a lubricative film that covers the vaginal wall. Additional moistening during intercourse comes from secretions of the paired greater vestibular or Bartholin's glands, although some believe that these glands have a more primal function of emitting an odiferous fluid to attract the male. In addition to lubricating, the vagina lengthens and dilates during sexual arousal as a result of relaxation of the vaginal wall smooth muscle. In human and animal models, sexual stimulation results in increased vaginal blood flow and decreased vaginal luminal pressure.[9,10]

Physiologic changes in the clitoris and vestibular bulbs during sexual arousal

With sexual stimulation, increased blood flow to the clitoral cavernosal and labial arteries resulting in increased clitoral intracavernous pressure, tumescence, and protrusion of the glans clitoris, and eversion and engorgement of the labia minora. Studies show that, unlike the penis, the clitoris and vestibular bulbs lack a subalbugineal layer between the erectile tissue and the tunica albuginea layer. In the male, this layer possesses a rich venous plexus that, during sexual excitement, expands against the tunica albiginea, reducing venous outflow and making the penis rigid. The absence of this venous plexus in the clitoris and vestibular bulbs suggests that this organ achieves tumescence, but not rigidity during sexual arousal.

Physiologic and biochemical mediators of the female sexual arousal response

Within the central nervous system, the medial preoptic, anterior hypothalamic region, and related libmic–hippocampal structures are responsible for sexual arousal. Upon activation, these centers transmit electrical signals through the parasympathetic and sympathetic nervous system. The neurogenic mechanisms modulating vaginal and clitoral smooth muscle tone, and vaginal and clitoral vascular smooth muscle relaxation are currently under investigation.

Nonadrenergic/noncholingeric mediated responses

Immunohistochemical studies in human vaginal tissues have shown the presence of nerve fibers containing NPY, VIP, NOS, CGRP and substance P.[11,12] Preliminary studies suggest that vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) are involved in modulating vaginal relaxation and secretory processes. In the clitoris, NO has been identified in human tissue and is hypothesized to be the primary mediator of clitoral and labial engorgement.[10] Organ bath analysis of rabbit clitoral cavernosal smooth muscle strips demonstrates enhanced relaxation in response to sodium nitroprusside and L-arginine (both NO donors), which supports the above hypothesis (Berman *et al*, unpublished data). Recently, phosphodiesterase Type V (PDE V), the enzyme responsible for degradation of cGMP has been isolated in human clitoral, vestibular bulb and vaginal smooth muscle culture, and is inhibited by sildenafil citrate.[9] Human and rabbit vaginal smooth muscle cells treated with the NO donor, sodium nitroprusside, in the presence of sildenafil, have enhanced intracellular cGMP synthesis and accumulation. PGE1 and forskolin also produced a marked increase in intracellular cGMP.[13]

In organ bath studies, sildenafil causes dose-dependent relaxation of female rabbit clitoral and vaginal smooth muscle strips (unpublished observation) further suggesting a role for NO as a mediator of clitoral cavernosal and vaginal wall smooth muscle relaxation. However, the exact identity of the relaxatory NANC neurotransmitter remains unclear. VIP is a nonadrenergic/noncholinergic neurotransmitter that like NO, may play a role in enhancing vaginal blood flow, lubrication, and secretions. The vagina is heavily innervated with VIP-immunoreactive nerve fibers in close relation to the epithelium and blood vessels.[14] In organ bath studies, VIP also causes dose-dependent relaxation of rabbit clitoral cavernosal and vaginal smooth muscle tissue, suggesting a similar role for endogenous VIP as a NANC neurotransmitter in clitoral and vaginal tissues (Berman *et al*, unpublished data).

Impact of hormones on female sexual function

Estrogen

Estrogen plays a significant role in regulating female sexual function. Estradiol levels affect cells throughout the peripheral and central nervous system and influence nerve transmission. A decline in serum estrogen levels results in thinning of vaginal mucosal epithelium and atrophy of vaginal wall

smooth muscle. Decreased estrogen levels also result in a less acidic environment in the vaginal canal. This can ultimately lead to vaginal infections, urinary tract infections, and incontinence as well complaints of sexual dysfunction.[15]

Estrogens also have vaso-protective and vasodilatory effects which result in increased vaginal and clitoral and urethral arterial flow resulting in maintenance of the female sexual response by preventing atherosclerotic compromise to pelvic arteries and arterioles.[16]

With menopause, and the decline in circulating estrogen levels, a majority of women experience some degree of change in sexual function. Common sexual complaints include loss of desire, decreased frequency of sexual activity, painful intercourse, diminished sexual responsiveness, difficulty achieving orgasm, and decreased genital sensation. Masters and Johnson[17] first published their findings of the physiologic changes occurring in menopausal women that related to sexual function in 1966. We have since learned that symptoms related to alterations in genital sensation and blood flow are, in part, secondary to declining estrogen levels, and that there is a direct correlation between the presence of sexual complaints and levels of estradiol below 50 pg/cm^3.[15]

Testosterone

Low testosterone levels are also associated with a decline in sexual arousal, genital sensation, libido, and orgasm. This can be accompanied by loss of pubic hair, vaginal mucosal thinning, and overall diminished sense of well being.[13,18] Therapeutic success with testosterone for inhibited desire in naturally menopausal women has been reported using a testosterone pellet.[19] Testosterone also reportedly improves sexual desire in women, who are postmenopausal secondary to oophorectomy.[20] There is evidence that testosterone supplementation decreases HDL levels and increases triglyceride levels, making women with history of hypercholesterolemia and cardiac disease at significant risk. Women with history of breast cancer should not be prescribed testosterone due to the fact that it can be converted to estrogen.

Etiologies of female sexual dysfunction

Vasculogenic

The recently named clitoral and vaginal vascular insufficiency syndromes are directly related to diminished genital blood flow secondary to atherosclerosis of the iliohypogastric/pudendal arterial bed.[21] Although other underlying conditions either psychological or physiological/organic may also manifest as decreased vaginal and clitoral engorgement, arterial insufficiency is one etiology that should be considered. Diminished pelvic blood flow secondary to aortoiliac or atherosclerotic disease leads to vaginal wall and clitoral smooth muscle fibrosis. This can ultimately result in symptoms of vaginal dryness and dyspareunia. Histomorphometric evaluation of clitoral erectile tissue from atherosclerotic animals demonstrates clitoral cavernosal artery wall thickening, loss of corporal smooth muscle and increase in collagen deposition.[9] In human clitoral tissue, there is a similar loss of corporal smooth muscle with replacement by fibrous connective tissue in association with atherosclerosis of clitoral cavernosal arteries.[9] While the precise mechanism is unknown, it is possible that the athersclerotic changes that occur in clitoral vascular and trabecular smooth muscle interfere with normal relaxation and dilation responses to sexual simulation.

Aside from atherosclerotic disease, alterations in circulating estrogen levels associated with menopause contribute to the age-associated changes in clitoral and vaginal smooth muscle. In addition, any traumatic injury to the iliohypogastric/pudendal arterial bed from pelvic fractures, blunt trauma, surgical disruption, or chronic perineal pressure from bicycle riding, for instance, can result in diminished vaginal and clitoral blood flow and complaints of sexual dysfunction.

Neurogenic

The same neurogenic etiologies that cause erectile dysfunction in men can also cause sexual dysfunction in women. These include: (1) spinal cord injury or disease of the central or peripheral nervous system, including, diabetes and (2) complete upper motor neuron injuries affecting sacral spinal segments. Women with incomplete injuries retain that capacity for psychogenic arousal and vaginal lubrication.[22] With regard to orgasm, women with spinal cord injury have significantly more difficulty achieving orgasm than normal controls. The effects of specific spinal cord injuries on female sexual response as well as the role for vasoactive pharmacotherapy in this population are being investigated. One recent report suggested a potential role for sildenafil in women with spinal cord injury.

Hormonal/endocrine

Dysfunction of the hypothalamic/pituitary axis, surgical or medical castration, menopause and

premature ovarian failure, and chronic birth control use are the most common causes of hormonally based female sexual dysfunction. The most common complaints associated with decreased estrogen and/or testosterone levels are decreased desire and libido, vaginal dryness, and lack of sexual arousal. Estrogen improves the integrity of vaginal mucosal tissue and has beneficial effects on vaginal sensation, vasocongestion, and secretions, which all leads to enhanced arousal. Estrogen deprivation causes a significant decrease in clitoral intracavenosal blood flow and vaginal and urethral blood flow.[3,16] Histologically, diffuse clitoral fibrosis, thinned vaginal epithelial layers, and decreased vaginal submucosal vasculature. Thus, a decline in circulating estrogen levels can produce significant adverse effects on structure and function of the vaginal and clitoris, ultimately affecting sexual function. Androgen deficiency in women is characterized by impaired sexual function, lessened well-being, loss of energy, and negative effects on bone mass. Testosterone, together with its metabolite dihydrotestosterone, is the most potent endogenous androgen in both men and women. It is also the major precursor of estrogens. During the reproductive years, testosterone levels fall substantially, and by the mid-40s, circulating testosterone levels are approximately half of those of women in their 20s. There is, however, no dramatic decrease at the time of spontaneous menopause. A major fall does occur following bilateral ovariectomy.[18]

Musculogenic

The pelvic floor muscles, in particular the levator ani and perineal membrane, participate in female sexual function and responsiveness. The perineal membrane, consisting of the bulbocavernosus and ischicavernosus muscles, when voluntarily contracted contributes to and intensifies sexual arousal and orgasm. In addition, they are responsible for the involuntary rhythmic contractions during orgasm. The levator ani muscles also modulate motor responses during orgasm as well as vaginal receptivity. When hypertonic, vaginismus can develop leading to or causing dyspareunia and other sexual pain disorders. When hypotonic, vaginal hypoanesthesia, coital anorgasmia as well as urinary incontinence during sexual intercourse or orgasm can develop.

Psychogenic

In women, despite the presence or absence of organic disease, emotional and relational issues significantly affect sexual arousal. Issues such as self-esteem, body image, and the quality of the relationship with her partner can all affect her ability to respond sexually. In addition, depression and other psychological and mood disorders are associated with female sexual dysfunction. Furthermore, the medications commonly used to treat depressions can significantly affect the female sexual response. The most frequently used medications for uncomplicated depression are the serotonin re-uptake inhibitors (SSRIs). Women receiving these medications often complaint of decreased desire, decreased arousal, decreased genital sensation, and difficulty achieving orgasm. Several studies have recently been published documenting improvement in SSRI-induced sexual dysfunction in women with sildenafil.[23]

Clinical evaluation of the female sexual response

Historically, evaluation of female patients with complaints of sexual dysfunction has been limited to psychological assessment. Physiologic evaluation of the female sexual response in the clinical setting has been complicated by the difficulty of objectively quantifying the changes that occur with arousal. Also, in contrast to the male erectile response, many genital changes that comprise the female sexual response are not only difficult to measure, but also may go unnoticed by the patient.

Medical/physiologic evaluation

Evaluation of the patient with sexual dysfunction should contain a thorough physical examination including a pelvic examination, psychological and psychosocial assessment, laboratory or hormonal studies as indicated and physiologic monitoring of measures of arousal. In this way, both subjective and objective measures can be obtained and evaluated. The suggested hormonal profile includes FSH, LH, prolactin total and free testosterone levels, SHBG and estradiol levels. Testosterone is bound to both albumin and serum hormone binding globulin (SHBG) in the blood. SHBG levels increase with age and decrease with administration of exogenous estrogens.[15,16] If an abnormal estrogen and/or testosterone level is documented, appropriate replacement therapy can be initiated with subsequent resolution or improvement of the patient's symptoms. Women with low estrogen and/or testosterone levels typically experience symptoms of decreased libido, decreased sensation, vaginal dryness, dyspareunia, and decreased arousal.

Medical conditions including those that disrupt the hypothalamic–pituitary axis or hormone deficiencies secondary to menopause, chemotherapy, or

Table 1

Treatment	*Company*	*Ingredient*	*Already used for*	*Bottom line/side effects*
Alista	Vivus Inc.	Topical Alprostadil/PGE 1	Male ED	Transient burning in men; in trials in women now
Androsorb (cream)	Novavax	Testosterone	Hormone-booster for hypogonadal men	Early stages of clinical trial; may heighten libido in postmenopausal women
EROS-CTD	Urometrics	Clitoral therapy device	New product	Increase sensation and blood flow to clitoris via gentle suction
Estratest (pill)	Solvay Pharmaceuticals	Estrogen–testosterone combination	Hormone replacement therapy (HRT)	Heightens libido in some women; side effects include acne and hair growth
Femprox (cream)	NexMed, Inc.	Blood vessel dilator	Erectile dysfunction	Improves blood flow to genitals; enhances arousal
Intrinsa (patch)	Proctor & Gamble Watson Laboratories	Testosterone	New product	In 6-month study women reported increased sexual activity and pleasure
Livial (pill)	Organon	Synthetic steroid	Osteoporosis HRT	Approved in Europe for menopause symptoms; improved mood and libido
NM1-870 (pill)	NitroMed	African tree bark fortified with nitric oxide	New product	Increases vaginal blood flow in postmenopausal women; may enhance arousal
Premarin or Estrace cream		Estrogen		Vaginal dryness and discomfort; not for use in women with history of blood clots or breast or endometrial cancer
Steryl-Norleucine VIP (cream)	SenetekPLC	Synthetic version of brain chemical	New product	Same as above
Testosterone creams	Off-label prescriptions from compounding Pharmacies	Testosterone		Not FDA approved Side effects include weight gain, hair growth, oily skin or enlarged clitoris
Tostrelle (gel)	Cellegy	Testosterone	Hormone-booster for hypogonadal men	Early study—testosterone levels in women on HRT jumped to levels of teenage girls
Uprima	Tap Pharmaceuticals	Apomorphine		Targets the brain and stimulates the release of dopamine. Side effects: nausea, vomiting, not yet FDA approved
Vagifem	Pharmacia Upjohn	Estrogen	New product	Improves dryness and irritation
Vasotem (tablet)	Zonagen	Blood vessel dilator	New product	Increases blood flow to genitals
Viagra	Pfizer	Blood vessel dilator	Male erectile dysfunction	Same as Vasotem

Sample treatments available and under investigation for Female Sexual Function complaints.

following bilateral salpingo-oophorectomies should be determined and medications that adversely effect sexual function should also be addressed and changed if not contraindicated (Table 1).

Evaluating the female sexual response in the clinical setting, both validates the patient's problem and potentially diagnoses organic disease such as vascular insufficiency, hormonal abnormalities, or neurologic disorders. The studies being undertaken at our institution seek to define ranges of normal for the following parameters:

(1) Genital blood flow: clitoral, labial, urethral, and vaginal peak systolic velocities and end diastolic velocities using Duplex Doppler Ultrasound.
(2) Vaginal lubrication measurements.
(3) Vaginal compliance/elasticity: pressure–volume changes.
(4) Genital sensation: vibration perception thresholds as well as temperature perception thresholds.

These measurements can be recorded at baseline and following sexual stimulation. Eventually, definition of the parameters prior to initiating medical therapy may become the standard of care.

Psychosocial/psychosexual assessment

In addition to the medical/physiologic evaluations, all patients should be evaluated for emotional and/or relational issues that may be contributing to her problem. This includes the context in which the patient experiences her sexuality, her self-esteem and body image, and her ability to communicate her sexual needs with her partner. This is an integral component of the female sexual function evaluation. Emotional and/or relational issues should be addressed prior to treatment, and certainly prior to determining treatment efficacy. If ongoing therapy is desired or required, it should also be provided.

To assess subjective sexual function, in particular sexual arousal, several instruments are available. The Brief Index of Sexual Function Inventory (BISF-W), for example, is a validated 21-item self-reported inventory of sexual interest, activity, satisfaction and preference and discriminates between depressed, sexually dysfunctional, and healthy patients. Subjective sexual response data reflect the personal experience of the patient, an important variable to evaluate because the ultimate goal is to enhance the personal sexual experience of the woman. Intervention is not considered successful unless the woman is able to subjectively experience sexual arousal, pleasure, and satisfaction. Thus, it is important to determine if physiological changes or improvement in blood flow, translate into an improved sexual experience. For instance, a physiologically documented increase in blood flow is irrelevant, unless the patient actually experiences increased arousal, sensation, and satisfaction reflected by those physiological processes.

Table 1 lists the latest drugs for women that show promise in treating sexual dysfunction problems. Some treatments are available now while others are still in the testing phases.

The ideal approach to female sexual dysfunction is a collaborative effort between therapists and physicians and should include a complete medical and psychosocial evaluation, as well as inclusion of the partner or spouse in the evaluation and treatment process. Although there are significant anatomic and embryologic parallels between men and women, the multifaceted nature of female sexual dysfunction is clearly distinct from that of the male. Thus, we cannot approach female patients or their sexual function problems in the identical fashion as male patients. The context in which a woman experiences her sexuality is equally if not more important than the physiologic outcome she experiences, and these issues should be determined before beginning medical therapy or determining treatment efficacies.

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