

Review Article

Neurologic Factors in Female Sexual Function and Dysfunction

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Sexual dysfunction affects both men and women, involving organic disorders, psychological problems, or both. Overall, the state of our knowledge is less advanced regarding female sexual physiology in comparison with male sexual function. Female sexual dysfunction has received little clinical and basic research attention and remains a largely untapped field in medicine. The epidemiology of female sexual dysfunction is poorly understood because relatively few studies have been done in community settings. In the United States, female sexual dysfunction has been estimated to affect 40% of women in the general population. Among the elderly, however, it has been reported that up to 87% of women complain of sexual dissatisfaction. Several studies have shown that the prevalence of female sexual arousal disorders correlates significantly with increasing age. These studies have shown that sexual arousal and frequency of coitus in the female decreases with increasing age. The pathophysiology of female sexual dysfunction appears more complex than that of males, involving multidimensional hormonal, neurological, vascular, psychological, and interpersonal aspects. Organic female sexual disorders may include a wide variety of vascular, neural, or neurovascular factors that lead to problems with libido, lubrication, and orgasm. However, the precise etiology and mechanistic pathways of age-related female sexual arousal disorders are yet to be determined. In the past two decades, some advances have been made in exploring the basic hemodynamics and neuroregulation of female sexual function and dysfunction in both animal models and in human studies. In this review, we summarize neural regulation of sexual function and neurological causes of sexual dysfunction in women.

Key Words: Arousal; Clitoris; Female; Nerve; Vagina

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ANATOMY OF THE FEMALE EXTERNAL GENITALS

The female genital organs consist of the labia majora, labia minora, clitoris, bulbs (of the vestibule), and vagina. While there are clearly many homologous structures in the male and female, the anatomy differs very significantly and should be described in its own right. Due to significant changes following menopause, many descriptions derived from cadaver dissection are inaccurate for younger and premenopausal women.

The *vulva* consists of the parts of the female genitals that are visible externally and include the labia majora, the labia minora, the glans of the clitoris, and the vestibule of the vagina. The *labia majora* represent the cleft female homo-

logue to the male scrotum. They are two symmetrical folds of skin filled with fat, connective tissue, nerves and lymphatic vessels. The lateral surface is covered with variable amounts of coarse hair while the medial surface is hairless and contains a large number of sebaceous glands. The function of the labia majora is to protect and enclose the vaginal vestibule. The labia minora are thin, delicate folds of vascular, fat-free, hairless skin located on each side of the vaginal vestibule. The labia minora divide anteriorly to form the prepuce and frenulum of the clitoris. The glans of the clitoris is described below. The *vestibule of the vagina* is the space enclosed by the labia minora and leads into the vagina itself. Anterior to the vestibule is the external urethral orifice and associated paraurethral (Skene's) glands. Posteriorly, the vestibule receives the orifices of the greater

vestibular (Bartholin's) glands, which provide lubrication for the vestibule of the vagina and are homologues of the bulbourethral glands of the male.

THE CLITORIS

The *clitoris* is a small midline erectile body that is homologous to the male penis. It consists of a glans, body, and crura. The glans is easily visible at the superior junction of the labia minora. The body, consisting of paired corpora with an incomplete septum between them, is 1 to 2 cm wide and 2 to 4 cm long [1]. The crura, 5 to 9 cm in length, are attached to the ischial bone and covered by the ischiocavernosus muscle [1].

1. Structural support

Like the penis, the clitoris is attached to the pubis by specialized connective tissue supports. The so-called *suspensory ligament of the clitoris* has both superficial and deep components [2]. There is a superficial fibro-fatty ligament that extends from within the fatty tissue of the mons pubis to the body of the clitoris and into the labia majora. In addition, there is a deep component that originates on the symphysis pubis itself, extends to the body of the clitoris and then to the bulbs of the clitoris. The supporting structures of the clitoris thus appear to function less as suspensory ligaments and more as traction ligaments that transmit force from the labia majora, bulbs, and vaginal introitus to the clitoris. Some authors have suggested that the anterior vaginal wall acts to transmit forces generated during intercourse to the clitoris [3].

2. Vascular supply

Blood supply to the body of the clitoris is supplied by paired pudendal arteries that course lateral to the urethra along the pelvic aspect of the anterior vaginal wall [1]. These arteries give off the cavernous artery and the artery to the bulb. The body of the clitoris is composed of cavernous tissue surrounded by tough tunica albuginea. However, the clitoris seems to lack the subalbuginea plexus characteristic of the penis [4]. This finding suggests that, unlike the penis, the clitoris does not have a well developed outflow occlusion mechanism and becomes erect mainly through increased blood flow.

3. Innervation and histochemistry

The glans of the clitoris forms a cap that sits on the ends of the corporal bodies and is richly innervated by sensory nerve endings [5]. The deep dorsal nerves perforate the glans on the dorsal aspect of its junction with the corporal bodies. Recent studies have confirmed that the dorsal nerve of the clitoris is relatively large (more than 2 mm in diameter) [1]. The cavernous nerve runs along with the cavernous artery as it enters the bodies of the clitoris. Nerves containing neuronal nitric oxide synthase have been detected in both the body and the glans of the human clitoris [6], suggesting that nitric oxide is involved in the control

of clitoral smooth muscle tone. Nerve fibers containing vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide (CGRP) and substance P (SP) have also been described in human clitoral tissue [7,8].

THE BULBS OF THE VESTIBULE

The female urethra, like the bulbous portion of the male urethra, is surrounded laterally by erectile tissue called the vestibular bulbs in most anatomy texts. Recent anatomic studies have shown that these erectile bodies are intimately related and lateral to the urethra rather than lateral to the vestibule of the vagina [1]. They are not, as often depicted in anatomic texts, located within the labia minora. Superiorly, the bulbs continue as the pars intermedia and terminate as the glans of the clitoris [9]. Thus, the bulbs represent the cleft female homologue to the bulb of the urethra in the male. The entire complex of spongy erectile tissue consisting of bulbs, pars intermedia, and clitoral glans correspond to the corpus spongiosum of the male [9].

THE VAGINA

1. Structure

The vagina is a muscular sheath that connects the uterus and the external genitalia. It has both sexual and reproductive functions and this dual function is reflected in various aspects of its structure, especially its vascular supply, its sensory and motor innervation and its marked distensibility. The wall of the vagina consists of an inner lining of stratified squamous epithelium, an intermediate layer of smooth muscle and an outer adventitial layer. The lining of the vagina is folded into numerous rugae which are related to its extreme distensibility. The vaginal entrance is closed by the bulbocavernosus muscle, a striated muscle.

2. Vascular supply

Corrosion studies of the rat vagina have shown that the vaginal epithelium is intimately related to a dense capillary network in the subepithelial layer [10]. This vascular network may be related to the production of transudate during sexual arousal. Somewhat deeper, the loose submucosal layer contains a complex of numerous large veins and smooth muscle fibers that resemble cavernous tissue. The smooth muscle layer consists of an inner circular layer and a strong external longitudinal layer. The adventitial layer consists of connective tissue and a large plexus of blood vessels.

3. Innervation and histochemistry

The vagina has a complex innervation that is not well understood. The pelvic nerves appear to subservise sensation from the vagina while the pudendal nerve subserves sensation from the labia and clitoris [11]. Afferent nerves in the vagina appear to contain substance P in both animal [11,12] and human [13] tissue samples, although SP-containing nerves appear to be sparse in the human vagina [13]. Nerves containing nitric oxide synthase (NOS) have

been demonstrated in animal [14] and human vaginas [15]. Nerves containing CGRP, neuropeptide Y, VIP, and peptide histidine-methionine (PHM) have also been found in the human vagina [15,16].

THE MECHANISM OF FEMALE SEXUAL AROUSAL RESPONSE

Female sexual arousal is a neurovascular phenomenon involving nerve-regulated vascular reactions. Neurovascular interactions during sexual arousal lead to several hemodynamic phases which affect simultaneously the clitoris, vestibular bulbs, and labia minora as well as the vagina. In the *resting phase*, the vagina is a sheath containing a potential space with a minimal blood flow and very low oxygen tension in the wall [17,18]. The earliest detectable sign of sexual arousal based on studies with experimental models is a significant increase in vaginal wall and clitoral blood flow [19]. There is a significant increase in clitoral cavernosal pressure as well [19]. With the onset of increased vaginal blood flow, production of vaginal transudate ensues [10, 20]. A significant rise in tissue oxygen tension follows about 20 seconds later which indicates increased inflow of arterial blood. In humans, vaginal and labial oxygen tension increases from 4 to 8 times baseline during sexual stimulation [17,18] and vaginal wall blood flow increases approximately threefold [21-23]. In humans, clitoral blood flow has been estimated to increase from 4 to 11 times baseline during sexual stimulation [24]. The increased blood flow reaches a plateau phase during which vaginal fluid transudate production continues. The final or resolution phase is characterized by the slow return of blood flow to baseline values. In women, up to 20-30 minutes is required for vaginal oxygen tension to return to baseline [17].

It is believed that the increase of clitoral intracavernosal and vaginal wall blood flow results in part from a decrease in vascular resistance and relaxation of clitoral cavernosal and vaginal wall tissues. The precise identity of the neurotransmitters that control vaginal blood flow is currently unknown. Atropine does not affect the pelvic nerve-stimulated rise in vaginal blood flow in animals [19,25] or the rise in vaginal blood flow seen in human females [26]. This evidence suggests that muscarinic neurotransmission is probably not involved. The ability of sildenafil to relax clitoral tissue and enhance nerve-stimulated vaginal blood flow has been reported [27,28]. This knowledge, of course, suggests the involvement of the NO-cyclic guanosine monophosphate (cGMP) pathway [27,29]. At the same time, it has been reported that administration of VIP, either intravenously or by injection in the vaginal wall, increases vaginal blood flow and induces vaginal fluid production [10,30]. Peptide histidine methionine (PHM) has effects similar to VIP but at lower potency [31]. Intravaginal prostaglandin E1 can also increase vaginal blood flow [32]. While some authors have stated that VIP is the primary neurotransmitter in the vaginal circulation [21,22], much more research in this area is required. A study with a rabbit model has shown that systemic ad-

ministration of apomorphine had no effect on basal clitoral intracavernosal and vaginal wall blood flow while significantly increasing blood inflow in these organs during nerve-stimulated vaginal and clitoral engorgement [32]. The precise mechanism by which apomorphine enhances nerve-stimulated but not basal clitoral intracavernosal and vaginal blood flow remains unknown. Apomorphine at concentrations of 0.1 mg/kg and 0.2 mg/kg was shown to be most effective in increasing nerve-stimulated clitoral intracavernosal and vaginal wall blood flows in the rabbit [32]. This may suggest the involvement of dopaminergic receptors in regulating the hemodynamic mechanism of clitoral and vaginal engorgement. Vaginal blood flow appears to undergo phasic shifts in conjunction with rapid eye movement (REM) sleep [33].

NEUROREGULATION OF FEMALE SEXUAL RESPONSE

1. Central mechanisms

Little is known about the central control of female sexual arousal. Sexual stimulation activates specific areas of the central nervous system such as the medial preoptic region, the anterior hypothalamic region, and the related limbic hippocampal structures. This stimulates transmission of signals via the parasympathetic and sympathetic pathways. The medial amygdala appears to be an important center that utilizes vasopressin as a central neurotransmitter [34]. Oxytocin is also clearly involved; oxytocin serum levels measured before and after sexual stimulation in 12 healthy women were significantly elevated [35]. Although intravenous apomorphine, a centrally acting dopaminergic agent, has been shown to cause increased peak clitoral and vaginal wall blood flow [32], the role of dopamine in female sexual behavior is not established.

2. Spinal mechanisms

The mechanism of genital arousal and orgasm during sexual stimulation involve spinal cord reflexes that are mediated by genital afferents originating from the pudendal nerve. Interneurons mediating these reflexes are known to be in a column in the central portion of the spinal gray matter. The efferent arm of the spinal reflexes involves sympathetic, parasympathetic, and somatic activity [36]. Studies with a rabbit model have shown that electrical stimulation of the vaginal branch of the pelvic nerve increases clitoral intracavernosal pressure and blood flow, vaginal wall pressure and blood flow, and vaginal length [19]. Afferent signaling during sexual stimulation enters the spinal cord in the sacral segments, which is then transmitted to supraspinal sites via the spinothalamic and spinoreticular systems [36]. The spinothalamic pathway contains myelinated fibers that end in the posterolateral nucleus of the thalamus, from which the signals are relayed to the medial thalamus. The precise reflex mechanisms of clitoral erection and vaginal engorgement are yet to be studied.

3. Peripheral mechanisms

The mechanism of vaginal engorgement during sexual arousal involves vasodilation and significant changes in vaginal tone. The vaginal tissue responds to sexual arousal by relaxing and lengthening [19]. Pelvic nerve-stimulated increased vaginal tone was abolished by atropine while vecuronium bromide, a striated muscle relaxant, prevented the subsequent fall in vaginal tension [37]. These results suggest that vaginal contraction may be under cholinergic control while vaginal lengthening or enlargement may relate to striated muscle contraction. How striated muscle contraction produces a decrease in vaginal pressure is unclear. It has been shown in humans that the distal part of the vagina contains more nerve fibers compared to the proximal part; likewise, the anterior vaginal wall is more densely innervated than the posterior wall [38]. Embryological origins of the proximal and distal vagina are also suggested to be different. The distal two-thirds of the vagina is suggested to be a derivative of the urogenital sinus whereas the proximal part is thought to originate from the uterovaginal primordium [39].

In the rabbit, stimulation of the vaginal branch of the pelvic nerve results in lengthening and dilation of the vagina that further leads to a lowering of vaginal luminal pressure and an increase in intravaginal wall pressure [19]. In rats, stimulation of the pelvic nerve causes a biphasic response in vaginal wall tension [37]. There is a rapid, short-lived increase in vaginal wall tension followed by a fall in tension to below the baseline value which is indicative of vaginal wall relaxation [19,37].

Organ bath studies with the rabbit vaginal tissue have shown that at baseline tension, electrical field stimulation (EFS) causes a biphasic contraction and relaxation response [40]. The alpha-2 adrenoceptor blocker yohimbine and the beta blocker propranolol were found to have little effect on vaginal tissue contraction in response to EFS and norepinephrine. Prazosin seemed to be significantly effective in inhibiting these contractile responses, suggesting that vaginal tissue contraction may be primarily mediated by the alpha-1 adrenoceptor [40]. Relaxation of the vaginal tissue appears to involve a non-adrenergic non-cholinergic (NANC) mechanism. The nature of the vaginal NANC neurotransmission remains controversial. The rabbit vaginal tissue relaxes after exposure to acetylcholine (Ach), vasoactive intestinal polypeptide (VIP), papaverine, and the nitric oxide (NO) donor nitroprusside in a concentration dependent manner [40]. VIP was found to be more effective in relaxing the vaginal tissue than the clitoral tissue [40]. The NO precursor L-arginine and the nitric oxide synthase inhibitor nitro-L-arginine (L-NNA) appeared to have little effect on vaginal tissue relaxation. Another study, however, found that NNA significantly inhibits the electrically-stimulated relaxation of rabbit vaginal tissue [41]. The authors performed immunohistochemical staining, which revealed marked eNOS and nNOS in the rabbit vagina. It was also found that estrogen treatment down-regulates eNOS and nNOS expression in the rabbit vagina

[41]. A VIP receptor antagonist has been shown to significantly increase the relaxation response to VIP while having little effect on EFS-induced relaxation of the vaginal tissue [40]. It has also been shown that nerve fibers in the vagina that run subepithelium and near the vascular bed are rich in VIP-immunoreactivity [42]. Human vaginal nerve fibers contain not only VIP and NOS but neuropeptide Y, CGMP, CGRP, and substance P as well [15]. Immunohistochemical staining has revealed the expression of five functional domains of the VIP precursor throughout the female human genital tract in neuronal elements closely related to the epithelial lining, perivascular tissue, and non-vascular smooth muscle [43].

Clitoral and penile smooth muscle appears to share a similar neuroregulatory mechanism. As in the human penis, immunohistochemical staining of human clitoral cavernosal tissue has revealed NOS subtype expression, suggesting the involvement of NO in the regulation of clitoral smooth muscle contractility and the development of clitoral engorgement [41]. Organ bath studies with the rabbit clitoral cavernosal tissue have shown that contraction of the clitoral tissue is primarily mediated by alpha-1 adrenoceptor [40]. Acetylcholine, VIP, papaverine, and the NO donor nitroprusside produce concentration-dependent relaxation in clitoral tissue as in penile tissue [40]. L-arginine significantly increases and NNA inhibits the clitoral relaxation to EFS and Ach, suggesting that endothelium-dependent and neurogenic relaxation of clitoral tissue may be mediated by NO. Another study showed that clitoral smooth muscle relaxation is enhanced by sildenafil, suggesting involvement of cGMP [27]. Angiotensin II has been shown to be a potent constrictor of rabbit clitoral smooth muscle in an organ bath. The clitoris has been shown to have angiotensin II receptors of the AT1 variety [44].

NEUROGENIC SEXUAL DYSFUNCTION IN WOMEN

Female sexual dysfunction has been categorized into problems with desire, arousal, orgasm, and pain [45-48]. *Sexual desire disorders* are sub-classified into hypoactive sexual desire disorders and sexual aversion disorders. *Hypoactive sexual desire disorder* is defined as persistent or recurrent lack of or absence of sexual fantasies and thoughts or desire for sexual activity. *Sexual aversion disorder* is a persistent or recurring fear, aversion to, and avoidance of sexual contact with a partner. *Sexual arousal disorder* is defined as the persistent or recurrent inability to achieve or maintain sexual excitement. This may be expressed as lack of excitement, lack of lubrication, lack of vaginal and clitoral engorgement, or lack of expression of other somatic responses. *Orgasmic disorder* is defined as the persistent or recurrent inability to achieve orgasm with sexual stimulation and arousal. *Sexual pain disorders* are sub-classified into dyspareunia, vaginismus, and other sexual pain disorders. *Dyspareunia* is defined as recurrent or persistent genital pain during sexual intercourse. *Vaginismus* is the recurrent or persistent involuntary spasm of outer vaginal muscu-

lature, which makes vaginal penetration difficult. Other sexual pain disorders include noncoital sexual pain, which is defined as recurrent or persistent genital pain caused by noncoital sexual stimulation. All types of sexual desire disorders are likely to lead to personal distress. Each category of female sexual dysfunction is divided to subtypes: chronic versus acquired, generalized versus situational, and organic versus psychogenic.

In contrast to the male, the pathophysiology of female sexual dysfunction is not easily categorized as vasculogenic, neurologic, or hormonal. Rather, it appears to involve multidimensional biologic, psychologic, and interpersonal aspects [49,50]. Sexual dysfunction in women correlates with age and with educational level [49]. The frequency of these sexual problems increases as menopause approaches and reaches a peak in the postmenopausal years [49,50].

Neurologic disorders are known to be associated with sexual dysfunction both in women and men. The role of neurologic factors in female sexual dysfunction, however, remains somewhat unexplored and may be undiagnosed. Many neurologic disorders, including autonomic and peripheral neuropathy, spinal cord injury, diabetic neuropathy, multiple sclerosis, and lumbar radiculopathy are likely to interfere with the neurophysiology of the female genital organs and lead to their dysfunction. It is believed that any neural lesion, central or peripheral, can interfere with the sensory and somatic component of the female genitals and lead to dysfunction. Dysfunction of the sensory fibers may interfere with the afferent signaling and sensory modalities that are quite important in female sexual response.

CENTRAL CAUSES OF FEMALE SEXUAL DYSFUNCTION

Central regulation of female sexual response has been explored to some extent. Central lesions are likely to interfere with female sexual physiology and lead to dysfunction. The precise mechanism by which central lesions affect female sexual function is yet to be determined. In general, it is believed that any central lesion would alter the efferent and afferent pathways of female sexual response leading to dysfunction.

SPINAL CAUSES

The relationship between spinal cord lesions and female sexual dysfunction has been frequently reported. In women, spinal cord injury may be associated with orgasmic and/or lubrication failure [51]. Arousal may be secondary to audiovisual stimuli, fantasy, or genital stimulation. In women with complete suprasacral spinal cord injury above T6, audiovisual stimuli fail to cause any change in vaginal pulse amplitude [52]. However, in women with preservation of sensory function in T11-L2 dermatomes, psychogenically-mediated genital vasocongestion is possible [53]. This suggests that, as in the male, the sympathetic outflow is an important

pathway for psychogenic genital response in the female.

Women with complete or incomplete suprasacral injury can achieve reflex genital response by manual stimulation but not when there is involvement of the sacral segments [54]. Orgasm is less likely in women with spinal cord injury and correlates poorly with the type of injury [53].

THE ROLE OF DIABETIC NEUROPATHY

Diabetes affects sexual function in both women and men. Diabetes mellitus, which is known to cause erectile dysfunction in men, may interfere with sexual function in women [55-58]. This issue, however, has been poorly investigated and it is unclear how diabetes leads to sexual disorders in women [59]. Female sexual dysfunction can be regarded as a silent complication of diabetes mellitus. Jensen studied the sexual function of 80 diabetic women and 40 non-diabetic women [58]. A significantly larger number of diabetic women (11 percent) complained of lack of orgasm compared with non-diabetic women (7.5 percent). A much greater number of diabetic women (24 percent) reported difficulty in achieving vaginal lubrication compared with non-diabetic women (8 percent). Within the diabetic group, the incidence of sexual dysfunction was much greater in women with diabetes-related peripheral neuropathy (44 percent) than in diabetic women without neuropathy. Another study showed that peripheral neuropathy closely correlates with sexual dysfunction in diabetic women [60]. Other studies have reported increased problems with vaginal lubrication in diabetic women [57,61]. Using vaginal photoplethysmographic measures of capillary engorgement, it has been shown that diabetic women demonstrate significantly less physiological arousal to erotic stimuli than controls, even though their subjective responses were comparable [62]. Biothesiometric examination has revealed that the sensation of the vaginal introitus, labium minora, and clitoris were markedly deteriorated in diabetic women compared with non-diabetic women [63].

Studies with a rat model of streptozotocin-induced diabetes have shown that diabetes impairs the relaxation responses of the vaginal tissue to EFS, to NO donors, and to calcitonin gene-related peptide (CGRP) [37]. It was also shown that diabetes impairs the contractile response of vaginal tissue to norepinephrine and to EFS. In the latter study, both the NO donors and CGRP inhibited EFS-induced contractions in diabetic and non-diabetic strips but the inhibition was found to be significantly lower in the diabetic group [37].

PERIPHERAL NEURAL FACTORS

Peripheral neurological disorders are known to be associated with sexual dysfunction in both women and men. Peripheral neuropathy is a common cause of erectile dysfunction but there is little relevant literature in females. Clitoral neuropathy has been observed to cause sexual dysfunction [64]. In a test of female genital pressure and touch

sensation, 32 neurologically intact women and 5 neurologically impaired women were tested [65]. A clear association was found between reduced vulvar sensitivity to pressure/touch and estrogen deficiency, sexual dysfunction, and neurologic impairment [65]. Postmenopausal and hypoestrogenic women had significantly reduced sensitivity to pressure/touch compared with premenopausal and normoestrogenic women, respectively [65].

Pudendal neuropathy as a complication of orthopedic surgery involving traction has been shown to induce sexual dysfunction [66]. This condition was found to be associated with signs of pudendal neurodegeneration and abnormal somatosensory evoked potentials of the pudendal nerve. Stretch neuropathy of the internal pudendal nerve and perineal nerve motor latency have been reported due to stretch injury of the pelvic musculature when the pelvic floor diaphragm is weak [67]. Perineal stretch neuropathy was found to closely correlate with the incidence of sexual dysfunction in women [67].

PSYCHOLOGICAL FACTORS

In women, psychological factors (history of sexual abuse, depression, anxiety, obsessive compulsive disorders), sociocultural issues (beliefs regarding sexual activity), and interpersonal issues (partner availability, partner function, relationship with partner, communication with partner) affect sexual function in all age groups [50,68]. With aging, additional psychological stresses may come to the fore, particularly loss of fertility, interruption of the menstrual cycle, and the start of postmenstrual changes. Recently, however, there has been a large cultural shift with respect to the negative implications of aging and menopause. The "baby boom" generation, in contrast to their mothers and grandmothers, believe that aging need not necessarily cause asexuality, poor health, and loss of productivity.

Conflicts of Interest

The authors have nothing to disclose.

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