

Vascular aetiology of female sexual arousal disorder (FSAD) in women: Evidence and diagnostic approach

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INTRODUCTION

The Report of the International Consensus Development Conference on Female Sexual Dysfunction (FSD) originally specified several types of difficulties regarding sexual arousability with the comprehensive definition of women's Sexual Arousal Disorder (1). This diagnosis could be further classified as lifelong versus acquired as well as generalized versus situational and, from an aetiological point of view, as organic, psychogenic, mixed or unknown (1).

Women's sexual arousal (SA) is a physiologic process primarily identified by genital vasocongestion, vaginal lubrication, enhanced local hyperaemia, increased vaginal length and vaginal pH, decreased vaginal luminal pressure as well as by the awareness of genital throbbing and tingling. SA involves the ability to attain and maintain adequate sexual excitement and it is gently modulated by psychosocial factors, hormonal milieu and several neurovascular inputs (2, 3).

Women's SA disorder is the persistent or recurrent inability to attain or maintain adequate sexual excitement causing personal distress. This disorder must consider the potential absence of coordination between an objective genital activation and/or extra-genital activation (i.e. skin sensitivity, mammary tension and increased scent perception towards pheromones) and the woman's subjective perception of the arousal itself (4).

Thus, due to these considerations, very recently a new classification system has been proposed, with the specific aim to subdivide the overall arousal disorder pattern into a) subjective SA disorder, b) genital SA disorder, c) combined genital and subjective arousal disorder as well as d) persistent SA disorder (5).

The aim of this section is both to distinguish few of the most frequent clinical vascular patho-physiological mechanisms of

genital FSAD and to suggest a practical specialized genital vascular diagnostic approach.

WOMEN'S SA DISORDERS: VASCULAR AETIOLOGY AND PATHO-PHYSIOLOGY

Physiological SA in women as well as in animals is strongly characterized by an increased autonomic activation. The latter seems to include both a parasympathetic blood flow component to genital and erectile tissues (namely, in the clitoris, labia and vaginal epithelium), and a sympathetic blood flow from the heart to striated and smooth muscles that participate in sexual responses. Moreover, during the last years the role of non-adrenergic, non-cholinergic (NANC) neurotransmitters/mediators [i.e. nitric oxide (NO)] in the arousal response have been studied with increasing interest. New in vivo models on rats, rabbits and dogs have made it possible to investigate vaginal and clitoral blood flow, vaginal oxygen tension, vaginal temperature and vaginal luminal pressure as markers of genital sexual arousal (6).

Genital hemodynamics results as the key point of the so-called women's genital arousal and normal hormonal milieu seem to represent a fundamental requisite to obtain a dynamic modification of the entire vasculature set throughout the arousal phase. Pre-clinical and clinical studies suggest that estrogens modulate genital hemodynamics and are critical for maintaining structural and functional integrity of vaginal tissues (7). Estrogen deprivation may lead to decreased pelvic blood flow resulting in diminished vaginal lubrication, clitoral fibrosis, thinning of the vaginal wall and decreased vaginal submucosal vasculature. Not many studies concern the effect of androgens over the genital blood flow and vasocongestion. Clinical studies have indicated that androgens modulate SA responses (8). While estrogens seem to strongly regulate the vascular components

of genital tissues, androgens markedly facilitate genital blood flow in estrogenized animals. Thus, it has been also suggested that androgens can contribute to genital arousal independently from a pure hemodynamics response to the clitoris and the vagina (8).

Women's SA is therefore also a hemodynamic process, involving increased arterial inflow, coordinated with clitoris smooth muscle relaxation, but it may be better defined as the final expression of a complex process involving sexual stimulation, ascending/descending steady control by the central nervous system (both supraspinally and spinally), a peripheral neurovascular pathway, and an important hormonal balance.

DIABETES MELLITUS AS A POTENTIAL GENITAL VASCULAR RISK FACTOR

A few manuscripts have underlined the significant role of diabetes (DM) in promoting women's sexual disorders (9). Neuropathy, vascular impairment and psychological problems have been showed as closely implicated in high rate of decreased libido, slow arousability, decreased vagina lubrication, orgasmic dysfunction and dyspareunia in women complaining of DM.

Recently, Enzlin et al. (10) reported data of a case-control study concerning prevalence and characteristics of sexual dysfunction in women suffering from type 1 DM, as compared with an age-matched control group of healthy women, demonstrating that significantly more women with diabetes (27%) than age-matched controls (15%) reported sexual dysfunction ($\chi^2=4.5$, $df=1$; $p=0.04$). Moreover, patients presented a higher prevalence of overall SA dysfunction ($\chi^2=3.8$, $df=1$; $p=0.05$) and of decreased lubrication ($\chi^2=6.5$, $df=2$; $p=0.04$) than healthy women. Interestingly, sexual problems were not isolated in occurrence; indeed, 11% in the studied group reported 2 or 3 sexual problems. Patients complaining of sexual disorders were not significantly differ-

ent in age ($p=0.13$), BMI ($p=0.08$), length of disease ($p=0.36$) or HbA_{1c} values ($p=0.47$) as compared with those without sexual complaints. Interestingly, this analysis did not show any statistically significant correlation between sexual complaints and peripheral neuropathy, autonomic neuropathy, nephropathy and retinopathy. In addition to what said before, the statistical analysis did not demonstrate any significant evidence due to the menopausal status ($p=0.59$) as well as the use of hormone replacement therapy or oral contraceptive pill ($p=0.37$).

Erol et al. (11) reported a reduced libido (77%), a diminished clitoral sensation (62.5%), while 37.5% complained of vaginal dryness and 41.6% described vaginal discomfort also in DM type 2 women.

We recently reported some preliminary results of a cross-sectional study aiming at evaluating prevalence and predictors of sexual dysfunction in both DM type 1 (58.3%) and type 2 (41.7%) women as compared with a control group of healthy age-matched controls asking for a yearly routine check-up visit at the Ob/Gyn clinic (12). While no significant differences have been found regarding the Female Sexual Function Index (FSFI)-arousal phase domain score, a direct comparison demonstrated that DM patients had worse score for the desire ($p<0.001$), the lubrication ($p<0.001$), and the orgasm ($p<0.001$) domains of the FSFI, as compared with the control group. The Beck's Inventory for Depression (BDI) showed that 48% of these patients had some degree of depression. The BDI score was significantly correlated with the arousal domain ($r= -0.54$; $p=0.003$), the orgasm domain ($r= -0.39$; $p<0.05$) as well as the satisfaction domain of the FSFI ($r= -0.48$; $p=0.04$).

A further analysis has been performed regarding the hormonal profile of the normal cycling women among the type 1 DM patients enrolled in the trial. Due to the potential significant role of the oestrogen balance in

promoting a normal genital blood flow, we considered the so-called "estrogenic basal tone" thus subdividing the patients into a group with estradiol (E2) ≥ 40 pg/ml (namely, women with a normal ovulatory cycle) and another one with E2 < 40 pg/ml (namely, not-ovulatory cycles). The direct comparison analysis demonstrated that DM women had lower E2 than controls both in the normal ovulatory and the not-ovulatory group. Moreover, DM women showed significantly ($p<0.05$) lower values for total and free testosterone, as well as for DHEA-S and delta 4-androstenedione. While the biologic role of these decreased values should be better defined, the reduction of circulating hormones might have a significant impact over the genital blood flow and the vaginal lubrication.

SEXUAL DYSFUNCTION IN WOMEN WITH CORONARY ARTERY DISEASE

While ED is a common and well known problem in men suffering from coronary artery disease (CAD), and may herald a systemic vasculopathic state, such as ischemic heart disease (IHD), at our knowledge investigations of sexual function and dysfunction in women with CAD are fewer and rarely complete.

To try to better evaluate both chronological, epidemiological and aetiological correlations between women's sexual dysfunction and CAD, from February 2001 we have enrolled 60 consecutive women presenting with angina pectoris at the emergency unit of our institution (13). A total amount of 30 (50%) out of the 60 patients [mean \pm SE age: 56 \pm 1.66 years] were ultimately enrolled in this still ongoing cross-sectional study and underwent a morphological and functional evaluation of the coronary arteries with a coronary angiography. Their FSFI results were thus compared with those of 102 age-matched consecutive women assessed for a yearly routine check-up at the Ob/Gyn clinic.

The overall prevalence of sexual dysfunction (SD) among these CAD women was 30% (9/30). 70.9% (7/9) of the CAD women complained of FSAD while a low lubrication score was reported by 8 (88.9%) out of these 9 women.

The direct comparison of the FSFI scores showed that the total-FSFI value was significantly higher ($p=0.02$) for controls than for women suffering from CAD. Patients also reported a significant higher amount of SA ($p=0.002$) as well as lubrication ($p=0.10$) disorders. Moreover, patients also had significantly lower ($p=0.01$) scores regarding the orgasmic phase domain of the FSFI. The BDI demonstrated that 33% (10/30) suffered from mild depression while severe depression interested 3 (10%) of the patients. Beck's score was significantly correlated with the FSFI-desire domain [$p=0.008$ ($r= -0.48$)] as well as with the arousal domain [$p=0.0005$ ($r= -0.64$)], the lubrication domain [$p=0.0008$ ($r= -0.63$)], the orgasm domain [$p=0.0004$ ($r= -0.66$)] and the overall sexual satisfaction domain [$p=0.0007$ ($r= -0.63$)]. Interestingly, FSD became evident prior to symptoms of ischemic heart disease in 7 (23%) out of the 30 patients. Therefore, 7 (78%) out of 9 patients in this series developed sexual disorders prior (median of 51 months; range: 12-96 months) to angina or a myocardial infarction. Although these findings need to be confirmed in a larger patient population, this preliminary report suggested that SD is an important health issue in women with CAD.

VASCULAR SPECIALIZED DIAGNOSTIC TESTING: A BRIEF COMPOUND

Diagnostic modalities such as vaginal photo-plethysmography, duplex Doppler ultrasound, vaginal and clitoral temperature and vibration sensory testing, and selective pudendal arteriogram expand the physician and patient understanding of the pathophysiological

mechanisms of FSAD, but, unfortunately, lack of normative data may limit the use of these specialized testing.

From a practical point of view, non-invasive vascular testing of women with SD, clinically useful in the everyday practice, includes vaginal photo-plethysmography and genital duplex Doppler ultrasound. Vaginal photo-plethysmography measures the vaginal pulse amplitude (VPA), reflecting phasic changes in vaginal engorgement with each heart beat providing quantitative data on the extent of vaginal vasocongestion (14). Several studies have already addressed its significance in a research setting; very recently, for instance, Basson and Brotto (15) elegantly demonstrated that women with photo-plethysmographic evidence of impaired genital arousal might also objectively benefit from sildenafil. Similarly, Laan et al. (14) conducted an objective study to demonstrate the effectiveness of tibolone in postmenopausal women by means of a vaginal photo-plethysmographic device. The authors showed that tibolone was effective in increasing VPA values when compared to placebo, that is to say to improve the vaginal hemodynamics during erotic stimulation. Likewise, the same study confirmed that tibolone increased both sexual desire in women, and frequency of excitement and vaginal lubrication compared to the placebo group.

The role of duplex Doppler ultrasonography in the management of women with SD remains to be determined. Historically Lavoiser et al. (16) reported data about the potential usefulness of the method and some practical suggestions. More recently a few investigators reported small patient series using duplex doppler ultrasound before and after stimulation (i.e., visual and vibratory, even in combination with topical application of 2% alprostadil) as a diagnostic tool in women with SD (17, 18). Nappi et al. (19), for instance, very recently used this diagnostic technique to objectively demonstrate that oral tibolone seemed to increase clitoral blood flow in post-

menopausal women complaining of both desire and genital arousal disorders. However, a standard technique is not yet available to maximize diagnostic information obtained by duplex doppler ultrasonography.

CONCLUSIONS

Genital women's sexual arousal dysfunction represents an important health issue and includes a broad spectrum of etiological disorders. As a parallel with the ED disorder in men, it might say that sometime FSAD should be considered as a symptom of clinically significant disease and life-threatening situations. Thus, sexual medicine absolutely needs a larger amount of clinical trials in this fascinating field.

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