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SEXUAL DYSFUNCTION IN FEMALE PATIENTS WITH DIABETES

Shiv Charan Navriya, Mch, Associate Professor, Department of Urology, All India Institution of Medical Sciences, Jodhpur, India. drshivnavriya2004@gmail.com

Manali Jain, Senior Resident, Department of Urology, All India Institution of Medical Sciences, Jodhpur, India. manalijain281996@gmail.com

Om Yadav, Senior Resident, Department of Urology, All India Institution of Medical Sciences, Jodhpur, India. omucite@gmail.com

Ravi Chandra Chowdary, Senior Resident, Department of Urology, All India Institution of Medical Sciences, Jodhpur, India. ravichanchowdary2628@gmail.com

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ABSTRACT

Female sexual dysfunction (FSD) is a significant complication of diabetes mellitus, affecting 20-80% of women with type 2 diabetes. The condition stems from multiple factors including vascular damage, neuropathy, hormonal imbalances, and psychological aspects. Sustained hyperglycemia leads to blood vessel damage and reduces nitric oxide bioavailability, affecting vaginal blood flow and lubrication. Management requires a comprehensive approach focusing on glycemic control, lifestyle modifications, and specific interventions including lubricants, medications, and psychological support. Treatment outcomes vary based on factors such as age, diabetes duration, and complication severity. Early intervention and regular screening are essential for improved outcomes.

INTRODUCTION AND EPIDEMIOLOGY

Female sexual dysfunction (FSD) represents a significant yet often overlooked complication of diabetes mellitus that substantially impacts quality of life and relationship satisfaction. Studies indicate that women with diabetes have a markedly higher prevalence of sexual dysfunction compared to normal women. In women with type 2 diabetes mellitus (T2DM), the prevalence of FSD is about 20–80%, compared to the general female population where it is about 40% (1). However, a recent study by Derosa et al. showed that the prevalence of FSD is about 87% (2). T2DM is a bigger burden in developed regions (Europe, North America), with approximately equal gender distribution (3). The relationship between diabetes and FSD is complex and multifactorial, involving physiological, psychological, and social components. Diabetes can affect sexual function through multiple pathways including vascular complications, neurological damage, hormonal imbalances, and psychological factors associated with a chronic disease. The duration of diabetes, glycemic control, and the presence of other diabetes-related complications all play crucial roles in the development and severity of FSD. Understanding these relationships is essential for healthcare providers to effectively address this important aspect of women's health in the context of diabetes care.

DEFINITION

The definition of female sexual dysfunction (FSD) includes female sexual interest/arousal disorder (FSIAD), female orgasmic disorder, and genitopelvic pain/penetration disorder. To be considered dysfunctional, these symptoms must cause distress and must occur at least 75% of the time over a 6-month period. This definition has been in place since the development of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) in 2013. Thus, incidence and prevalence data based on this definition are developing (4) Prevalence of FSD is seen in women of reproductive age, which also include perimenopausal women although menopausal and postmenopausal women are also affected by FSD. Female Sexual Dysfunction is classified as Primary (occurring independently without medical or psychiatric causes) or Secondary (resulting from medical conditions, psychiatric disorders, or medications/ substances) (5).

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

The World Health Organization (WHO) declared human sexuality to be part of health quality and well-being in 1974 (WHO meeting on education and treatment in human sexuality) (6). In women, sexual function depends on different physiological circumstances such as vaginal hemodynamics and neurologic innervation, and the activity of genital and pelvic structures (7). Female sexual dysfunction in women with diabetes stems from decreased clitoral blood flow due to vascular damage and peripheral neuropathy affecting the hypo gastric- vaginal/clitoral arterial bed. Despite these known mechanisms, research remains limited, with most studies having small sample sizes and focusing on specific factors rather than comprehensive analysis (8). Blood vessel damage from diabetes is a major cause of sexual problems in both men and women. Underlying atherosclerosis may be suggested by measuring two enzymes called paraoxonase-1 (PON-1) and arylesterase (ARE), which are usually lower in diabetic patients with blood vessel problems (9). PON is an enzyme that helps break down harmful substances, particularly one called paraoxon. PON comes in three forms (PON-1, PON-2, and PON-3). Low levels of PON-1 signal various health problems, including diabetes, heart disease, kidney problems, arthritis, metabolic issues, or thyroid dysfunction (10). PON-1 and ARE contribute to the protective effect of HDL against atherosclerosis. A study by Ciftci and colleagues observed a negative correlation between PON-1 activity and erectile dysfunction (ED), along with a correlation between PON-1 activity and HDL levels, while LDL levels were higher in the ED group compared with the control group (11).

When blood glucose levels stay high for a long time, it damages cells in two main ways: by creating advanced glycation end products (AGEs), and by causing oxidative stress. This damages blood vessels and nerves that are important for the sexual response. High blood glucose also makes the vagina dry and more prone to infections, which can make sex uncomfortable. Research shows that keeping blood glucose levels steady and well-controlled can help prevent or reduce these sexual problems (12). There are some studies that correlate better glycemic control with lower incidence of FSD and better outcomes (13).

In diabetes, endothelial damage makes it harder for blood vessels to relax and allow proper blood flow during sexual arousal. This happens because nitric oxide causes vasodilation and in patients with diabetes reduced nitric oxide bioavailability and reduced endothelial signaling hinder normal blood vessel relaxation during sexual excitation, resulting in decreased vaginal blood flow and lubrication. At the same time, diabetes harms nerves in the genital area, reducing sensation and natural sexual responses. Both issues together make sexual function more difficult (14).

Dyspareunia in postmenopausal women primarily stems from genitourinary syndrome of menopause (GSM), characterized by progressive vulvovaginal atrophy due to estrogen deficiency. The decline in estrogen leads to thinning of vaginal epithelium, reduced elasticity, decreased lubrication, and increased vaginal pH. These changes result in symptoms including vaginal dryness, burning, irritation, and pain during intercourse. This condition affects postmenopausal women and often goes underreported and undertreated. Unlike vasomotor symptoms, GSM is progressive and doesn't resolve without intervention. The impact on sexual function can be significant, leading to reduced sexual activity, relationship strain, and decreased quality of life.

T2DM frequently causes hormonal abnormalities, which might contribute to sexual dysfunction. Insulin resistance and hyperinsulinemia affect the hypothalamic–pituitary–ovarian axis, altering sex hormone levels (mainly estrogen) and to lessor degree progesterone and testosterone. Women with androgen excess and males with androgen insufficiency have the same cardiometabolic characteristics. The proper balance of estrogens and androgens is critical for maintaining energy metabolism, body composition, and sexual function. These changes can lead to diminished sexual desire, vaginal dryness, and poor genital responsiveness. (15)

Many women report a combination of symptoms that may worsen with poor glycemic control and duration of diabetes. The interaction between physiological changes and psychological factors, such as diabetes-related stress, body image concerns, and relationship dynamics, creates a complex clinical picture that requires comprehensive evaluation and management (figure 1).

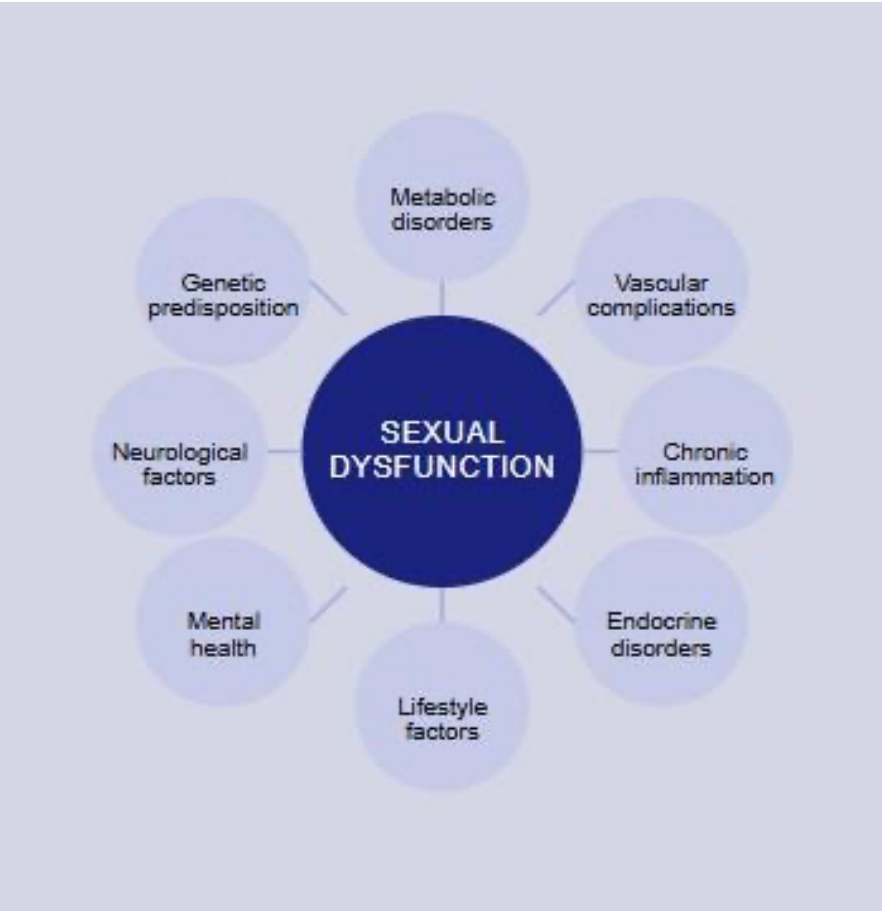

Figure 1. Proposed mechanisms of FSD in patients with Type 2 DM.

DIAGNOSIS AND ASSESSMENT

A systematic approach to diagnosing FSD in women is essential for effective management. The diagnostic process should begin with a detailed medical history, including diabetes control, complications, medications, and comorbidities. Sexual history should be obtained sensitively, addressing the nature and timeline of sexual concerns, relationship factors, and impact on quality of life. Validated assessment tools such as the Female Sexual Function Index (FSFI) (16), the Sexual Function Questionnaire (16), female Orgasm Scale (17), and Multidimensional Vaginal Penetration Disorder Questionnaire (18) can provide objective measures of sexual dysfunction and help monitor treatment outcomes. Physical examination should include evaluation of vaginal health, signs of neuropathy, and vascular status. Laboratory assessments should include glycemic control markers (HbA1c), hormonal status (especially in perimenopausal women), and screening for other endocrine disorders that may contribute to sexual dysfunction. Psychological assessment is crucial, as depression, anxiety, and diabetes-related distress frequently co-exist with FSD. The diagnostic process should also consider cultural and social factors that may influence sexual function and help-seeking behavior. Healthcare providers should maintain a non-judgmental, culturally sensitive approach while conducting these assessments to ensure accurate diagnosis and appropriate treatment planning.

DIFFERENT DOMAINS OF FEMALE SEXUAL DYSFUNCTION

Sexual dysfunction (SD) is classified by two main medical systems (19):

1. DSM (The Diagnostic and Statistical Manual of Mental Disorders)
2. ICD (International Classification of Diseases), version 11

3. Both systems organize sexual problems based on the natural stages of sexual activity, from initial arousal through to orgasm. The conditions are divided into four main groups of sexual disorders (20).

DOMAIN 1: DESIRE PROBLEMS

- Definition: Persistent lack of sexual thoughts/fantasies
- Types:
    - Hypoactive Sexual Desire Disorder (HSDD)
    - Sexual Aversion Disorder (SAD)
- Assessment Tool: Sexual Function Questionnaire (SFQ-V1) (16)

DOMAIN 2: AROUSAL ISSUES

- Definition: Problems with physical/mental sexual excitement
- Symptoms: Poor genital response, lack of interest
- Assessment Tool: Female Sexual Function Index (FSFI) (16)

DOMAIN 3: ORGASM DIFFICULTIES

- Types:
    - Primary: Lifelong inability
    - Secondary: Acquired problem
- Definition: Absent/delayed/reduced orgasms
- Assessment Tool: Female Orgasm Scale (17)

DOMAIN 4: PAIN CONDITIONS

- Definition: Pain during sexual activity
- Symptoms:
    - Pelvic muscle spasms
    - Entry pain
    - Fear of penetration
- Assessment Tool: Multidimensional Vaginal Penetration Disorder Questionnaire (18)

Female sexual dysfunction classifications have evolved significantly. Recent systems (ICSM, ISSWSH, ICD-11) separate desire from arousal issues and emphasize sexual distress as crucial for diagnosis. ICD-11 introduced a new sexual health chapter, while experts have defined new subtypes of arousal disorders (FCAD, FGAD) (19,20) (table 1).

Table 1. The Main Classifications of Female Sexual Dysfunction					
ICD		**DSM**	**ICSM**	**ISSWSH**	
ICD-10	ICD-11(PROPOSED)	DSM-V	Fourth ICSM	ISSWSH-2016	ISSWSH-2018
Lack or loss of sexual desire	Hypoactive sexual desire disorder	Female sexual interest/arousal disorder	Hypoactive sexual desire dysfunction	Hypoactive sexual desire disorder	Hypoactive sexual desire disorder
Sexual aversion	Recommended for deletion	Female orgasmic disorder	Female sexual arousal dysfunction	Female genital arousal disorder	Female sexual arousal disorder: -female cognitive arousal disorder -female genital arousal disorder
Lack of sexual enjoyment	Female sexual arousal dysfunction	Genito-pelvic penetration disorder	Female orgasmic dysfunction	Persistent genital arousal disorder	Persistent genital arousal disorder
Failure of sexual response			Female genital-pelvic pain dysfunction	Female orgasm disorder	Female orgasm disorder
Orgasmic dysfunction	Orgasmic dysfunction		Persistent genital arousal disorder	Female orgasmic illness syndrome	Female orgasmic illness syndrome
Non organic vaginismus	Sexual pain penetration disorder		Postcoital syndrome(post-orgasmic illness syndrome)		

TREATMENT STRATEGIES AND MANAGEMENT

Management of FSD in women requires a comprehensive, individualized approach addressing the underlying diabetes-related factors and specific sexual concerns. The cornerstone of treatment is optimizing glycemic control through appropriate diabetes management, as improved metabolic control often correlates with better sexual function. Lifestyle modifications, including regular exercise, smoking cessation, and stress reduction, can improve glycemic control and sexual health.

Specific treatments for sexual dysfunction may include vaginal moisturizers and lubricants for vaginal dryness, pelvic floor physical therapy for dyspareunia, and medications to address specific sexual concerns where appropriate. Hormonal therapy may be considered in post-menopausal women after careful risk assessment. For female sexual dysfunction in

diabetes, treatments include PDE-5 inhibitors. Studies using animal models of female sexual response suggest the physiological effects of PDE5 on vaginal and clitoral tissues are similar to those observed in males (figure 2); therefore, it is unlikely that the lack of effects of PDE5 on women's sexual functioning could be related to gender differences in the physiological effects of PDE5. NO synthase (NOS) is active in the vaginal epithelium, and the PDE5 enzyme has been identified in vaginal smooth muscle tissue and the clitoral shaft (21). The various PDE5 inhibitors that have been evaluated in clinical trials in this population have included sildenafil, tadalafil, vardenafil, udenafil, mirodenafil and avanafil (21,32).

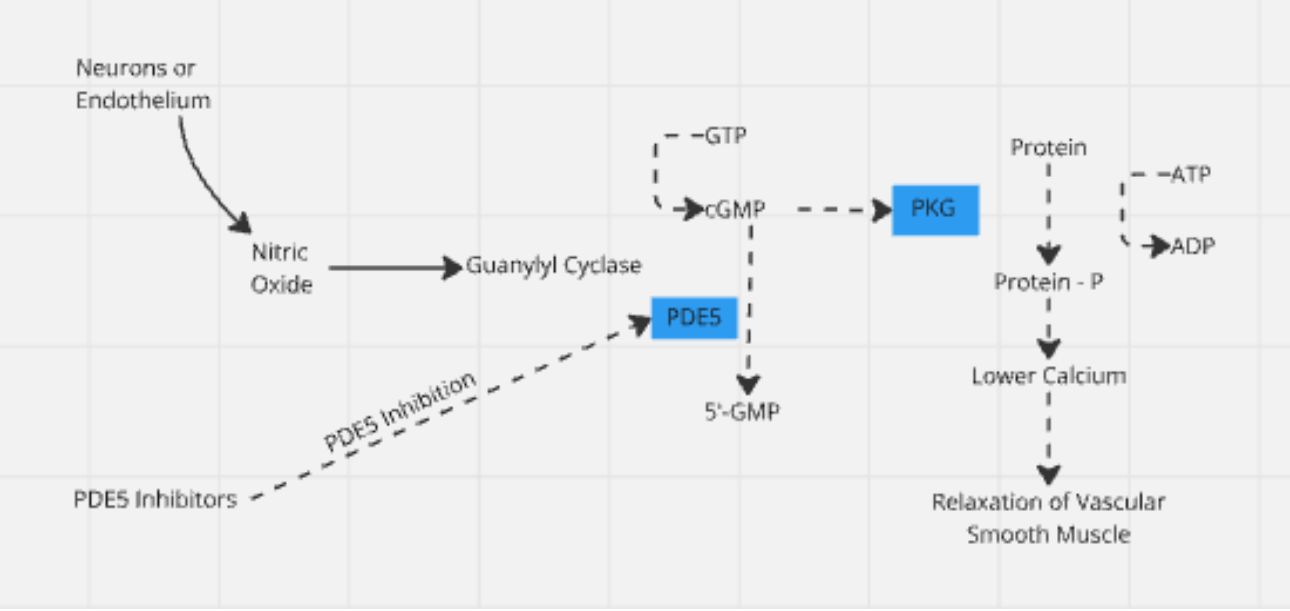

Figure 2. Mechanism of PDE-5 in Female Sexual dysfunction.

Blood flow for better arousal and orgasm, while topical estrogen treatments address vaginal dryness and tissue health. Sexual aids such as vibrators or other similar devices can be beneficial for some women in enhancing sexual pleasure (21,22). Psychological interventions, including cognitive behavioral therapy, sex therapy, and relationship counseling play vital roles in addressing the psychological aspects of FSD. Management of concurrent conditions such as depression, anxiety, and other diabetes complications is essential. Patient education about the relationship between diabetes and sexual health, along with strategies for maintaining intimate relationships despite chronic illness, should be integrated into the treatment plan. Regular follow-up is necessary to monitor progress and adjust interventions as needed.

PREVENTION, PROGNOSIS, AND FUTURE DIRECTIONS

Prevention of FSD in women focuses on maintaining optimal glycemic control, early detection of complications, and addressing modifiable risk factors. Regular screening for sexual concerns should be integrated into routine diabetes care to enable early intervention. The prognosis varies depending on multiple factors including age, duration, severity of diabetes, presence of complications, and effectiveness of interventions. Research suggests that early intervention and comprehensive management can improve sexual function and quality of life for many women (23). Emerging areas of research include novel therapeutic approaches such as growth factors

for vaginal health, new drug delivery systems, and innovative psychological interventions.

Pharmacological strategies include ospemifene, a selective estrogen receptor modulator, that has been shown to be effective for the treatment of vulvovaginal atrophy in postmenopausal women with vaginal dryness (24) or flibanserin, a 5-HT1A agonist/5-HT2A antagonist, for women with hypoactive sexual desire (25) Future directions in management may involve personalized medicine approaches based on individual risk factors and response patterns. Additionally, there is a growing recognition of the need for better integration of sexual health care into diabetes management programs and improved training for healthcare providers in addressing these concerns. The development of new assessment tools and treatment modalities specifically tailored for diabetic women with FSD continues to be an active area of research. Understanding the long-term outcomes of various interventions and identifying factors that predict treatment success remain important goals for future studies.

Table 2. Recent Advances in Pharmacotherapy For FSD

Drug name	**Flibanserin (26.27)**	**Bremelanotide (27,28)**	**Testosterone (Off-label) (27,29,30)**	**Ospemifene (31)**	**PDE5 Inhibitors (32)**
Brand Name	Addyi	Vyleesi	Various	Osphena	Viagra , Cialis
Indication	Premenopausal HSDD	Premenopausal HSDD	Postmenopausal sexual dysfunction • Low libido • Used off-label in US	Moderate-severe dyspareunia and VVA in postmenopausal women	• SSRI-induced FSD • Diabetic FSD • Arousal disorders
Administration	100mg oral daily at bedtime	1.75mgSC injection 45 min before activity; max 8/month	• Various formulations • Creams, gels, implants • 0.5-2% of male doses	60mg oral daily with food	Viagra: • Start 25mg 1-2 hours before activity Cialis: • 2.5-5mg daily
Mechanism	• 5-HT1A agonist • 5-HT2A antagonist • Modulates serotonin, dopamine, norepinephrine	Melanocortin-4 receptor agonist	Androgenic effects on sexual response and libido	• SERM • Vaginal estrogen agonist • Breast estrogen antagonist	FIG 2
Common Side Effects	• Dizziness • Somnolence • Nausea • Hypotension	• Nausea (40%) • Flushing • Injection site reactions • Headache	• Acne • Hirsutism • Voice changes • Clitoral enlargement	• Hot flashes • Vaginal discharge • Muscle spasms • Hyperhidrosis	• Headache •Flushing • Nasal congestion •Dyspepsia • Visual changes
Contraindications	• Alcohol use • Hepatic impairment • Hypotension	• Uncontrolled hypertension • CVD • hypersensitivity	• Active breast cancer • Severe liver disease • Pregnancy	• Abnormal bleeding • Estrogen-dependent neoplasia • Active DVT/PE • Arterial thromboembolism	• Nitrate use •Hypotension • Recent stroke/MI • High-risk cardiac disease

Drug Interactions	• CYP3A4 modulators • CNS depressants • Alcohol (severe)	• Limited • Caution with antihypertensives	• Anticoagulants • Insulin • Corticosteroids	•CYP3A4/2C9/2C19 inhibitors • Estrogens • High-fat meals affect absorption	• Nitrates • Alpha blockers • Strong CYP3A4 inhibitors • HIV protease inhibitors
Monitoring Needs	• BP monitoring • Liver function • Alcohol use	• BP monitoring • Nausea management	• Testosterone levels • Lipids • Liver function • CBC • Breast exams	• Annual gynecologic exam • Abnormal bleeding • Thromboembolic symptoms	• BP monitoring • Nausea monitoring
Best Use Case	Premenopausal women who can abstain from alcohol	Premenopausal women who prefer on-demand treatment	Postmenopausal women with low T and no contraindications	Postmenopausal women with VVA who can't use vaginal estrogen	•SSRI-induced FSD • Diabetic FSD • Arousal disorders
FDA approved	In 2015, flibanserin became the first agent to gain approval from the U.S. Food and Drug Administration (FDA) for the treatment of HSDD	A newly approved pharmaceutical option for treatment of HSDD in premenopausal women	The off-label use of testosterone to increase sexual desire in postmenopausal women is supported by evidence as well as several professional societies.	Approved by the FDA for the treatment of dyspareunia (painful intercourse) in postmenopausal women	Not FDA approved for FSD

ASSOCIATION OF FSD IN TYPE 1 DIABETES MELLITUS

Female sexual dysfunction (FSD) in Type 1 diabetes mellitus represents a complex clinical challenge affecting reproductive health, quality of life, and intimate relationships. The condition encompasses multiple sexual health disorders including decreased libido, arousal difficulties, orgasmic dysfunction, and dyspareunia (33).

The pathophysiological mechanisms are intricate and interconnected:

Vascular Changes: Chronic hyperglycemia causes endothelial dysfunction and reduced nitric oxide production, leading to decreased vaginal and clitoral blood flow. This impairs arousal response and natural lubrication, often resulting in vaginal dryness and discomfort during intercourse.

Neurological Impact: Diabetic neuropathy affects both autonomic and peripheral nervous systems. Autonomic neuropathy disrupts sexual response by impairing genital blood flow regulation and vaginal lubrication. Peripheral neuropathy reduces genital sensation, affecting arousal and orgasmic capacity.

Hormonal Alterations: Type 1 DM can affect hypothalamic-pituitary-ovarian axis function, potentially leading to irregular menstruation and altered sex hormone levels. This may contribute to reduced libido and vaginal atrophy.

Psychological Factors: Women with Type 1 DM often experience higher rates of depression, anxiety, and poor body image, which significantly impact

sexual desire and satisfaction. The burden of disease management and fear of complications can create psychological barriers to intimate relationships.

Treatment Considerations: Management requires a comprehensive approach including:

- Optimal glycemic control
- Regular screening for complications
- Psychological support
- Sexual health counseling
- Treatment of specific symptoms (e.g., lubricants for vaginal dryness)
- Partner involvement in treatment planning

Early recognition and intervention are crucial for preventing progression and maintaining sexual health in women with Type 1 DM.

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