Association Between Infertility and Sexual Dysfunction in Men and Women

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ABSTRACT

Introduction: The relation between infertility and sexual dysfunction can be reciprocal. Causes of sexual dysfunction that affect fertility include erectile dysfunction, Peyronie's disease (abnormal penile curvature), low libido, ejaculatory disorders in men, and genito-pelvic pain/penetration disorder (GPPPD) and low sexual desire in women.

Aim: To review the association between infertility and sexual dysfunction and discuss current management strategies to address sexual disorders in couples with infertility.

Methods: Peer-reviewed publications from PubMed published from 1980 through February 2016 were identified that related to sexual dysfunction and infertility in men and women.

Main Outcome Measures: Pathophysiology and management approach of erectile dysfunction, Peyronie's disease, low libido, ejaculatory disorders in men, and GPPPD and low sexual desire in women and how each etiology contributes to sexual dysfunction and infertility in the couple.

Results: Treating the infertile couple with sexual dysfunction involves addressing underlying conditions such as psychogenic erectile dysfunction, low testosterone, Peyronie's disease in men, and GPPPD and low sexual desire in women. Psychogenic erectile dysfunction can be successfully treated with phosphodiesterase inhibitors. Low testosterone is often identified in men with infertility, but testosterone therapy is contraindicated in men attempting conception. Men with Peyronie's disease have a new treatment option to address their penile curvature—collagenase *Clostridium histolyticum* injection directly into the penile plaque. GPPPD is a broad disorder that includes vulvodynia and vaginismus and can be treated with topical lubricants and moisturizers. We must address psychosocial factors in women with low sexual desire. Flibanserin and transdermal testosterone (off-label) are novel therapies for women with low sexual desire.

Conclusion: Sexual dysfunction in a couple with infertility is a complex issue. Management of infertility and sexual dysfunction should involve appropriate medical therapy and addressing the psychosocial concerns of the couple.

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Key Words: Erectile Dysfunction; Peyronie's Disease; Hypogonadism; Vulvodynia; Vaginismus; Hypoactive Sexual Desire Disorder

INTRODUCTION

Infertility is defined as the failure to conceive after 12 months of unprotected intercourse in women younger than 35 years or after 6 months of unprotected intercourse in women older than 35.[1] Infertility affects up to 15% of couples[2] and is a significant life stressor comparable to chronic illness or the loss of a loved one.[3] In addition to personal stress, infertility puts immense stress on a relationship, because the individuals in the relationship begin to place blame on themselves and on each other. With the degree of stress associated with infertility, it is no surprise that infertility is frequently associated with sexual dysfunction.

Sexual dysfunction is grouped into four general categories: sexual desire, arousal, orgasmic, and pain disorders. Sexual desire

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disorders are further divided into hypoactive sexual desire disorder and sexual aversion disorder. Sexual arousal disorders are grouped based on whether they occur in men or women. In men, sexual arousal disorder commonly manifests as erectile dysfunction (ED), whereas in women, it manifests as inadequate lubrication in response to sexual stimulation. Sexual pain disorders are split into dyspareunia (men or women) or vaginismus (women only) in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*). In the updated *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM 5*), the definition of sexual dysfunction was altered to reflect more recent studies in sexual behavior. Highlights from the changes include having a diagnostic classification that differs between men and women, merging desire and arousal into a single diagnosis called *female sexual arousal disorder,* and grouping dyspareunia and vaginismus under one diagnosis of genito-pelvic pain/penetration disorder (GPPPD), among numerous other taxonomic changes.[4] Sexual function in a couple should be considered as part of a dyadic unit. If one individual in the couple has sexual dysfunction, the other individual can harbor feelings of guilt or lower self-esteem. For example, women whose partners have ED report decreased sexual satisfaction.[5] Hence, similar to infertility, sexual dysfunction in one individual in a relationship affects the couple as a whole.

Although infertility and sexual dysfunction in a couple can occur in isolation, the two disorders are frequently linked. Childbearing is an integral component of many partnerships and the inability to conceive often leads to sexual difficulty. An infertile couple might associate sexual intercourse with anger, guilt, and depression, and sex becomes a means of trying (and failing) to reproduce, as opposed to a connection between the two partners.[6] This begets further sexual dysfunction, which decreases the chances of successful conception. The concept works reciprocally; men and women with sexual dysfunction simply might be unable or less able to participate in sexual activity, which negatively affects the fertility of the couple.

Thus, a cyclical relation between sexual dysfunction and infertility exists. However, select causes of sexual dysfunction directly affect fertility and include ED, Peyronie's disease (PD), low sexual desire, and anejaculation in men and GPPPD and low sexual desire in women. In this review, we discuss different types of sexual dysfunction and their impact on and associations with infertility. We examine the most common causes of sexual dysfunction and infertility and explore current management strategies.

EPIDEMIOLOGY

Infertility often is a disorder of young people, because the elderly (particularly women) generally do not try to conceive. However, in reproductive-age men and women, infertility increases in incidence with age. In the National Survey of Family Growth, 6.0% of women in the cohort reported infertility, with a much higher prevalence in older women of reproductive age, with 27% of women 35 to 44 years old reporting infertility.[7] In another study focused only on women 15 to 44 years old, infertility was observed in 15.5%, with older women, those with lower education, and those with a history of gynecologic disorders being the most affected.[8] However, these studies do not comment on common causes of infertility. Although up to 50% of cases of infertility involve the male and female partners,[9-11] in a study of 8,500 infertile couples, female factor infertility was identified in 37% of couples. The most common identifiable female factors were ovulatory disorders (25%), endometriosis (15%), pelvic adhesions (12%), tubal blockage (11%), other tubal abnormalities (11%), and hyperprolactinemia (7%). Unknown factors contributed to 19% of infertility attributable to the female partner.[12]

Although men can maintain fertility into older age, evidence supports aging of the male reproductive system and age-related decrements in male fertility. Based on the National Survey of Family Growth study, 9.4% of men 15 to 44 years old and 12% of men 25 to 44 years old reported infertility of some cause.[7] The causes of male infertility can be categorized using four main categories: disorders of sperm transport such as retrograde ejaculation or anejaculation, endocrine disorders, genetic disorders, and idiopathic causes. Disorders of sperm transport account for 10% to 20% of cases of male infertility.[13] Endocrine disorders include primary (1%−2%) and secondary (10%−20%) hypogonadism. Known genetic disorders account for up to 30% of cases of male infertility, and the most commonly implicated abnormalities are Y chromosome microdeletions, monogenic disorders, and cytogenetic disorders.[14] Idiopathic causes account for up to 40% of cases of male infertility.[15] However, because spermatogenesis is a complex process involving the integration of a multitude of genes, genetic aberrations might be implicated in a significant proportion of cases of idiopathic male infertility.[16]

Infertility is a common complaint, but sexual dysfunction is even more prevalent in the general population. Based on the National Health and Social Life Survey (NHSLS), 43% of women reported sexual dysfunction.[17] A study by the Global Study of Sexual Attitudes and Behaviors (GSSAB) specifically explored the prevalence of sexual dysfunction in women. The results from this survey further corroborated the NHSLS data, with the most common complaints being low sexual desire (26%−43%) and anorgasmia (18%−41%).[18] However, neither the NHSLS nor the GSSAB included personal distress as a component of their criteria for sexual dysfunction. However, the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking study later included personal distress in the definition of sexual dysfunction, finding the overall prevalence of sexual dysfunction to be consistent with the NHSLS and GSSAB results. However, when incorporating sexual distress into the definition, sexual dysfunction was found in only 12% of women.[19] Regardless of the definition used, multiple publications have consistently shown the widespread prevalence of female sexual dysfunction.

Table 1. Causes of infertility and sexual dysfunction in men

Sexual dysfunction	Male infertility	Infertility and sexual dysfunction
Depression	Sperm production defects	Erectile dysfunction
Medications	Varicocele	Peyronie's disease
Orgasmic dysfunction	Sperm function or transport	Low sexual desire
Lifestyle and environment	Anejaculation	
	Hypogonadism	
	Known genetic disorders	
	Cryptorchidism	
	Cancer	
	Idiopathic infertility	
	Hypospadias	

Similar to female sexual dysfunction, male sexual dysfunction is a common complaint. According to the NHSLS, 31% of men reported sexual dysfunction.[17] Male sexual dysfunction progressively worsens with age. In the 1994 Massachusetts Male Aging Study, approximately 40% of men 40 years old had impaired sexual function.[20] In a follow-up study, sexual function was found to sharply decline in men in each decade after 50 years of age.[21]

PATHOPHYSIOLOGY AND MANAGEMENT OF MALE INFERTILITY

Management of infertility involves addressing the individual pathologies present in the male and/or female partner. Successful treatment of the infertile man, when considering sexual dysfunction, relates directly to the underlying pathology. To diagnose underlying male pathology, male patients should be assessed with a comprehensive medical and sexual history, a complete physical examination (especially a genitourinary examination), and laboratory evaluation, if necessary. The most common causes of male sexual dysfunction affecting fertility include ED, PD, low sexual desire, and anejaculation (Table 1).

Erectile Dysfunction

ED is one of the most common causes of sexual dysfunction, and the prevalence of ED is higher in infertile men than in the general population.[22] ED is often multifactorial, involving organic and psychogenic factors.[23] Understanding whether ED is psychogenic or organic is essential to providing appropriate treatment. However, it should be understood that virtually all cases of ED have psychogenic and organic components, with the psychogenic component having a variable impact on the severity of the disease. Assessing for reversible causes also is important in approaching ED. Certain medications, such as selective serotonin re-uptake inhibitors (SSRIs), can cause ED, so switching from one antidepressant to another with fewer sexual side effects, such as bupropion, can help. Similarly, cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes mellitus, are linked to ED. Treating these underlying medical conditions can slow or reverse the progression of ED.[24,25]

If a psychogenic component of ED predominates, psychotherapy and a daily low-dose phosphodiesterase type 5 inhibitor (PDE5i) often are effective.[26] For organic etiologies of ED, first-line treatment using a PDE5i, such as sildenafil, vardenafil, tadalafil, or avanafil, is appropriate. All these PDE5is have equivalent efficacy, although tadalafil has the longest half-life and avanafil has a more rapid onset of action than the others.[27]

If PDE5 is are not effective, vacuum-assisted erection devices or intracavernosal injection of vasoactive drugs is often second-line therapy. Vacuum-assisted erection devices are less invasive than intracavernosal drugs but are generally associated with lower satisfaction rates for the patient and the partner.[28] Intracavernosal injection of alprostadil (Edex; Actient Pharmaceuticals, LLC, Lake Forest, IL, USA; Caverject Impulse; Pfizer, New York, NY, USA) is the only intracavernosal injection approved for ED by the Food and Drug Administration; and although efficacy rates are high, adverse effects include penile pain and, rarely, priapism.[23] Because of the potential side effects of alprostadil monotherapy, many clinicians use a tri-mix (alprostadil, papaverine, and phentolamine) or a bi-mix (papaverine and phentolamine). Tri-mix has the highest efficacy rate of the drugs used for intracavernosal injection but nevertheless can cause penile pain, although at a lower frequency compared with alprostadil monotherapy. Although the efficacy of bi-mix is lower than that of tri-mix, the incidence of penile pain is lower because there is no alprostadil in the mixture to affect a prostaglandin-mediated pain response. Intraurethral alprostadil is another option, particularly in patients who prefer a less invasive option to self-injections. Although less invasive, intraurethral alprostadil is less efficacious than intracavernosal alprostadil.[23] Placement of a penile prosthesis represents a permanent solution to ED and is the treatment of choice in men who do not respond to first- and second-line therapies (Figure 1).

Peyronie's Disease

PD results in fibrotic plaques of the penile tunica albuginea, which can lead to pain and penile deformity during erection. Penile deformity resulting from PD can lead to dyspareunia in the male and female partners, contributing to fertility difficulties.

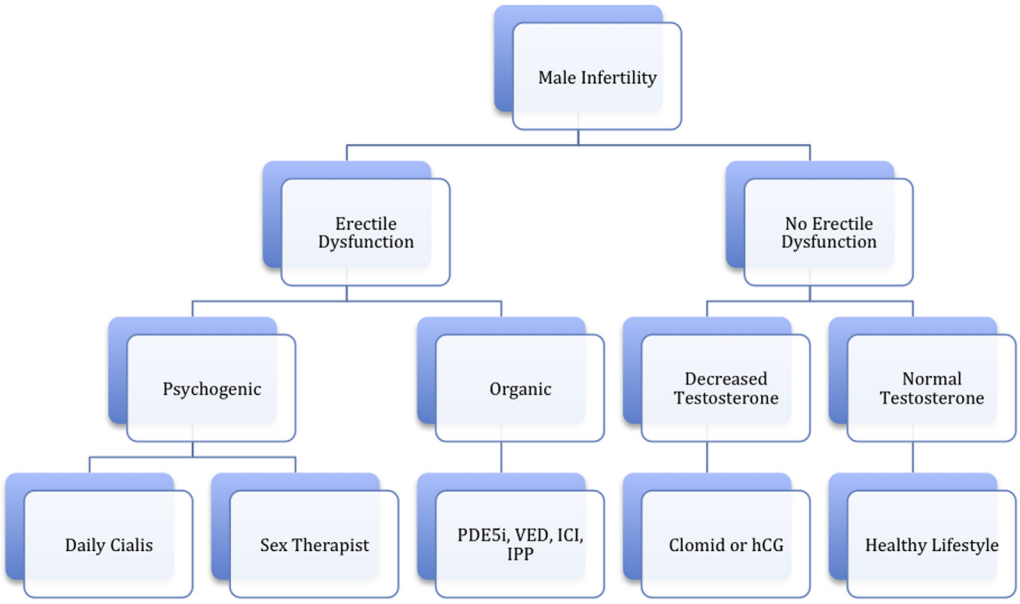

Figure 1. Management algorithm for erectile dysfunction. ICI = intracavernosal injection; IPP = inflatable penile prosthesis; PDE5i = phosphodiesterase type 5 inhibitor; VED = vacuum-assisted erection device. Figure 1 is available in color at www.smr.jsexmed.org.

The pathophysiology of PD can result from repeated mild trauma to the penis, which incites bleeding into the subtunical spaces.[29] The bleeding results in a local inflammatory response, resulting in progressive fibrotic plaque formation.[30,31]

An important consideration when evaluating a patient with PD is whether pain is present. If pain is present during an erection or at baseline, then the current treatment suggested by the most recent American Urological Association guidelines is the use of non-steroidal anti-inflammatory drugs.[32] If the patient does not have pain and the deformity is stable, then the degree of deformity should be objectively assessed. If the curvature is less than 30°, then observation is acceptable. If the curvature is greater than 30° but less than 90°, then medical intervention with intralesional collagenase *Clostridium histolyticum* (Xiaflex; Auxilium Pharmaceuticals, Inc, Chesterbrook, PA, USA) is indicated (Figure 2).[33] The evidence supporting the efficacy of *C histolyticum* is based on two randomized controlled trials, which showed significant improvement in penile curvature in the treatment groups compared with placebo.[34]

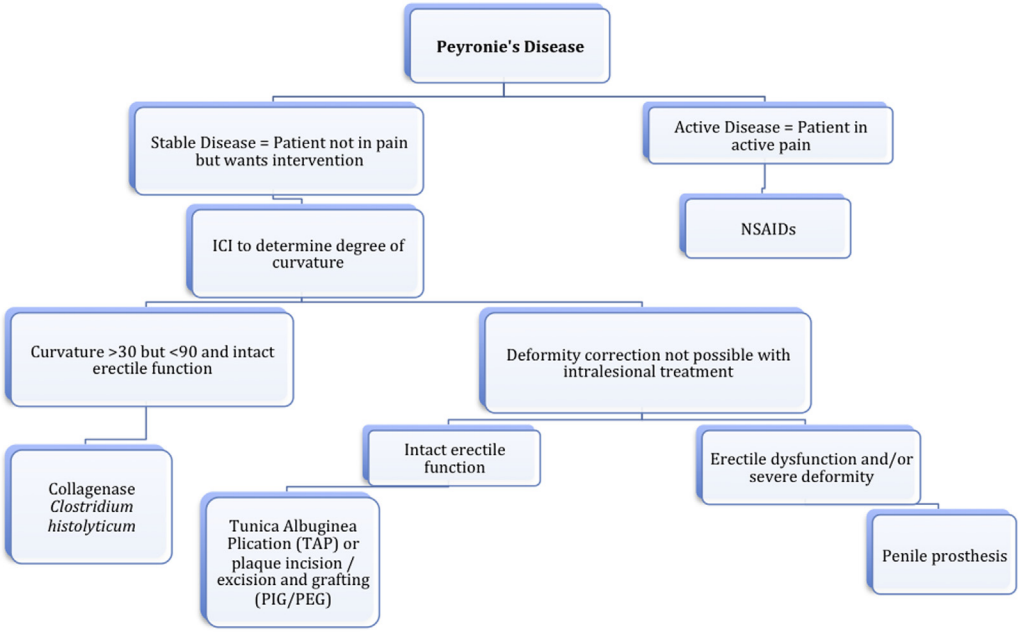

Figure 2. Management algorithm for men with Peyronie's disease. ICI = intracavernosal injection; NSAID = non-steroidal anti-inflammatory drug. Figure 2 is available in color at www.smr.jsexmed.org.

If severe penile deformity is observed, or if the patient is unresponsive to medical therapy, then surgical intervention is the gold standard.[33] There are numerous surgical approaches, ranging from simple plication to incision or excision of the plaque with grafting.[35] However, before surgical correction of penile deformity, erectile function must be assessed to further inform the surgical approach. In some men, placement of a penile prosthesis with penile modeling, rather than mere plication or plaque incision or excision and grafting, is more effective.[33,36] All surgical approaches have a high success rate, with few lasting side effects.[37]

Low Sexual Desire or Hypogonadism

Hypogonadism, diagnosed by the presence of hypogonadal symptoms and low serum testosterone levels, is linked to infertility and sexual dysfunction. With age, there is a decrease in testosterone and an increase in SHBG in men, which can result in decreases in bone density, muscle strength, and libido and in ED.[38] Hypogonadism also has been implicated in the development of metabolic syndrome in men.[39]

Primary hypogonadism, which represents an abnormality at the testicular level and is diagnosed in the presence of low testosterone with increased gonadotropin levels (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), can be acquired through mechanisms such testicular injury, tumors, or infections[40] or can represent congenital abnormalities, such as Klinefelter syndrome, cryptorchidism, or myotonic dystrophy. The congenital abnormalities are generally challenging to treat, although there have been recent advances. For example, in Klinefelter syndrome, seminiferous tubules are destroyed, which results in significantly decreased sperm production. However, sperm extraction techniques have shown success in facilitating fertility in otherwise hopelessly infertile couples. Microdissection testicular sperm extraction can be highly successful in men with Klinefelter syndrome. In one study, men with normal baseline testosterone levels (>300 ng/dL) had a sperm retrieval rate of 86%, whereas men with testosterone levels lower than 250 ng/dL who received medical therapy to increase testosterone levels also had a high retrieval rate. Clinical pregnancy and live birth rates were 57% and 45% in those cohorts, respectively.[41] Even if men with Klinefelter syndrome cannot achieve viable pregnancies with their partners, they do benefit from testosterone therapy through effects on virilization, energy, and libido.

In men with secondary hypogonadism, diagnosed in the presence of low testosterone with low or inappropriately normal gonadotropin levels, the testicles function normally, but a defect in the hypothalamic-pituitary-gonadal axis, generally in the hypothalamus or anterior pituitary, exists.[42] Secondary hypogonadism can be caused by hyperprolactinemia through prolactin's inhibitory action on gonadotropin-releasing hormone, thus leading to decreased LH and FSH secretion by the pituitary. Hyperprolactinemia is a side effect of some medications, particularly antipsychotics, through their antagonistic effects on dopaminergic D2 receptors.[43] Discontinuing these medications will restore prolactin and testosterone levels. Hyperprolactinemia also can result from pituitary adenomas, which should be treated with a dopamine agonist, such as bromocriptine or cabergoline.

Secondary hypogonadism also can be a consequence of hypothalamic disease. In these men, gonadotropins are used to increase intratesticular testosterone to improve fertility. Exogenous testosterone is not given to men with hypogonadism if fertility is a goal, because it will inhibit normal testicular function and decrease fertility.[44] Instead, treatment can start with human chorionic gonadotropin 1,500 to 2,000 IU three times per week. Patients are given human chorionic gonadotropin because it mimics LH activity but is more stable, has a longer half-life, and can stimulate intratesticular testosterone production from Leydig cells, resulting in improved spermatogenesis.[45] Therapy with human chorionic gonadotropin is titrated to achieve a serum testosterone concentration of 400 to 800 ng/dL and sperm counts are measured every 1 to 3 months. If the sperm count does not reach 5 million to 10 million/mL, then human menopausal gonadotropin is added, which is used because of its FSH contribution (Figure 3). Another treatment in hypogonadotropic men, including commonly in men with Kallmann syndrome, (idiopathic hypogonadotropic hypogonadism) that has shown success is pulsatile gonadotropin-releasing hormone.[46] Although pulsatile gonadotropin-releasing hormone does more closely follow normal human hormonal physiology,[47] it requires patients to wear portable pumps, which can be inconvenient.

Clomiphene citrate (Clomid; Upsher-Smith Laboratories Inc, Maple Grove, MN, USA) is a commonly used (although off-label) drug in treating male infertility. It is a selective estrogen receptor modulator that acts by inhibiting negative feedback of estrogen on the hypothalamus and anterior pituitary, resulting in upregulation of the hypothalamic-pituitary-gonadal axis and thus increasing FSH and LH levels and increasing testosterone levels. Although clomiphene citrate improves testosterone levels and can improve sexual function,[48] its effects on male infertility are not as well established. In a review of nine clinical studies conducted by Willets et al,[49] Clomid was found to have a statistically significant benefit on pregnancy in only one study. Although there were no adverse effects of long-term Clomid use, the reviewers concluded there was no benefit of Clomid use in the setting of male infertility. In a more recent meta-analysis, Chua et al[50] proposed the use of clomiphene citrate as empiric medical therapy in men with idiopathic infertility, because it increases pregnancy rate and improves sperm concentration and motility.

Ejaculatory Dysfunction

Anejaculation is another cause of infertility and a common sexual dysfunction in men. In the evaluation of a man with anejaculation, determination of whether the patient can still experience orgasm is important. Most men with ejaculatory disorders still experience orgasm,[51] and in men who are orgasmic, but anejaculatory, one must next distinguish retrograde ejaculation from

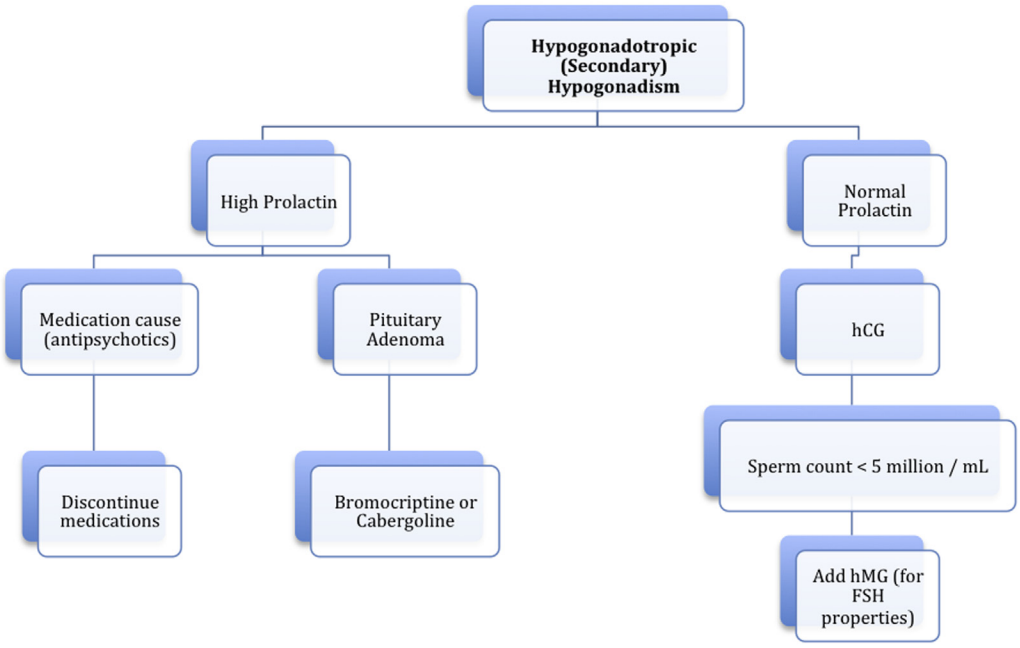

Figure 3. Management algorithm for men with secondary hypogonadism. FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin. Figure 3 is available in color at www.smr.jsexmed.org.

complete failure of seminal emission, which is performed using a post-orgasm urinalysis (Figure 4). In the absence of sperm in the urine, absence of seminal emission is assumed.

If retrograde ejaculation is present, then it is most commonly predisposed to by diabetes mellitus, retroperitoneal lymph node dissection, bladder neck surgery, and transurethral resection of the prostate.[52] First-line therapy for retrograde ejaculation is pharmacologic, with the use of sympathomimetics—such as pseudoephedrine—to facilitate bladder neck closure. If the patient has a structural cause for retrograde ejaculation, this is

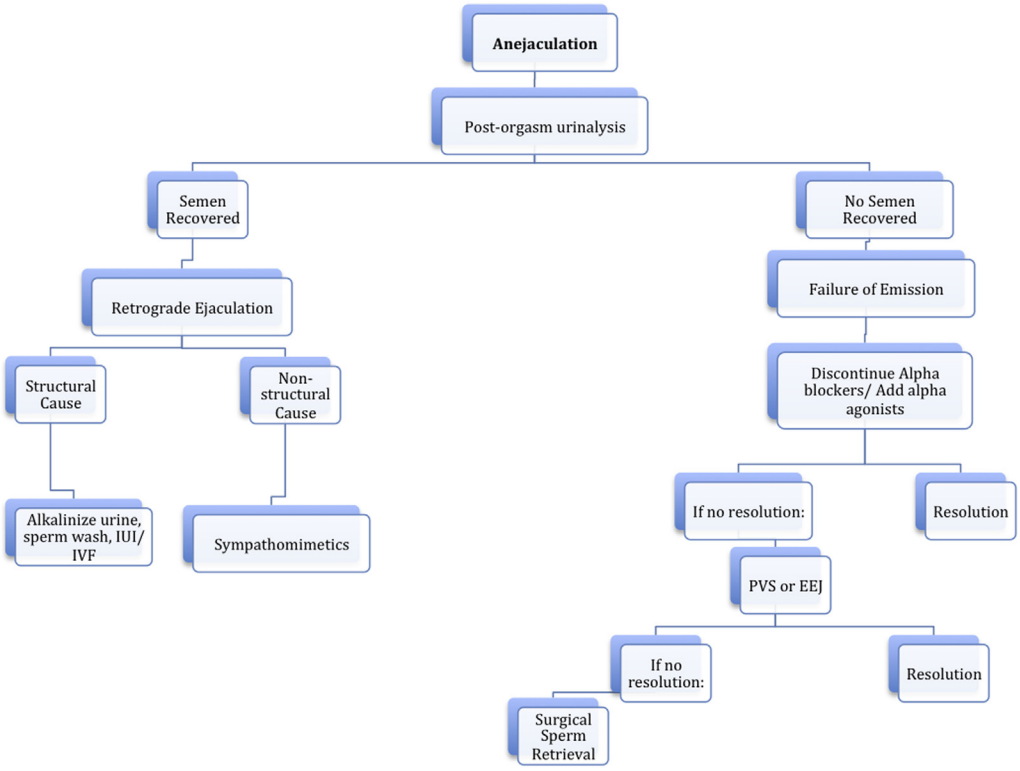

Figure 4. Management algorithm for men with anejaculation. EEJ = electroejaculation; IUI = intrauterine insemination; IVF = in vitro fertilization; PVS = penile vibratory stimulation. Figure 4 is available in color at www.smr.jsexmed.org.

generally irreversible.[52] However, pregnancy can still be achieved in these cases by alkalinizing the patient's urine followed by sperm washing and intrauterine insemination or in vitro fertilization with intracytoplasmic sperm injection.[53,54]

Failure of emission is generally from damage to sympathetic nerve pathways to the bladder neck and ejaculatory system,[55] which can result from neurovascular injury from prostatectomy, retroperitoneal lymph node dissection, or spinal cord injury.[56] Other causes include anatomic defects in the ejaculatory apparatus and medications such as α-adrenergic antagonists (ie, tamsulosin).[55] If failure of emission persists after discontinuation of any offending drugs, then pharmacologic therapy using α-adrenergic medications might be helpful.[55] If pharmacologic therapy fails and the couple desires pregnancy, then penile vibratory stimulation (PVS) and electroejaculation (EEJ) have shown success, particularly in patients with anejaculation owing to spinal cord injury. Use of PVS restores antegrade ejaculation in 86% of patients with spinal cord injury at levels T10 and higher.[57] EEJ is successful at restoring ejaculation in almost all men with spinal cord injury at any level, although there is a higher incidence of retrograde ejaculation in EEJ compared with PVS.[57] If PVS and EEJ fail to yield any ejaculate, surgical sperm retrieval is used in an attempt to restore fertility, although this commits a couple to in vitro fertilization or intracytoplasmic sperm injection.[57]

Ejaculatory dysfunction in relation to infertility also must include evaluation for premature ejaculation (PE). Although the definition of PE has evolved during the past century, recently the International Society for Sexual Medicine defined it as "a male sexual dysfunction characterized by (i) ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration from the first sexual experience or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less; (ii) the inability to delay ejaculation on all or nearly all vaginal penetrations; and (iii) negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy."[58] The definition demonstrates how PE has a negative impact on fertility. Ejaculation that occurs before vaginal penetration is a direct barrier to fertility because the sperm fails to enter the vagina and fertilize the ovum. Furthermore, the stress PE places on the couple can lead to tension in the couple and ultimately to lack of sexual activity.[59]

There are four main subtypes of PE: lifelong PE, acquired PE, variable PE, and subjective PE.[60] Lifelong PE generally involves an intravaginal ejaculatory latency time (IELT) of less than 1 minute and ejaculation is too early for almost every episode of intercourse starting from approximately the first sexual experience. IELT is shortest in lifelong PE and thus has the most negative impact on fertility. It has been suggested that the etiology of lifelong PE is related to genetic alterations in serotonin (5-HT) neurotransmission. Pharmacotherapy is the best management strategy for lifelong PE.[61] Acquired PE has an IELT of 1 to 2 minutes, and the man's ejaculatory response is normal for most of his life. The development of acquired PE can be attributed to comorbid medical conditions or psychogenic causes; thus, the best management strategy is a combination of pharmacologic therapy and psychotherapy.[61] In variable PE, IELT can be normal or diminished or completely lacking, with the best management approach focused on psychotherapy. Subjective PE is associated with an IELT of 5 to 20 minutes, which can be normal or even long. The key to this diagnosis is simply that the man's complaint of PE is a subjective complaint.

Changes in 5-HT neurotransmission have been implicated in PE, and studies have shown that men with PE benefit from increases in 5-HT in the synaptic cleft.[62] Thus, first-line agents for PE include SSRIs, many of which also have a well-described side effect of delayed ejaculation. The most commonly used SSRIs in the management of PE are dapoxetine, fluoxetine, paroxetine, sertraline, citalopram, and escitalopram.[61] All these agents are used off-label as treatment for PE, aside from dapoxetine, which is the only currently approved drug for PE in Europe. Dapoxetine has an advantage over other SSRIs because of its shorter half-life and is short-acting, making it more effective for more rapid treatment.[63] Other off-label drugs used for PE include tramadol (opioid antagonist), PDE5is, most notably sildenafil and vardenafil, and clomipramine (tricyclic antidepressant), which have been shown to prolong IELT vs placebo.[64-66] Topical treatments also have shown to be effective. Agents that have been studied include sodium sulfacetamide cream, lidocaine-prilocaine cream and spray, and dyclonine combined with alprostadil.[61]

PATHOPHYSIOLOGY AND MANAGEMENT OF FEMALE SEXUAL HEALTH ISSUES AND THEIR IMPACT ON FERTILITY

There is a unique interrelation between sexual dysfunction and infertility in that sexual dysfunction can be a cause and a consequence of infertility. The main causes of sexual dysfunction implicated in infertility are female sexual interest and arousal disorders and sexual pain disorders currently classified as GPPPD (Figure 5, Table 2). With these disorders, intimacy and coital activity are decreased or interrupted, and fertility is compromised. When left ignored and untreated, it is clear these conditions can deeply affect relationships, health, and overall quality of life.

Female Sexual Desire and Arousal Disorder

Lack of sexual desire is the most prevalent sexual dysfunction in women. In the *DSM-IV-TR,* it was known as *hypoactive sexual desire disorder;* and in the more recent *DSM-5,* the terminology was updated to *female sexual interest and arousal disorder.* To meet criteria for diagnosis, women must have at least three of the following symptoms: loss or decrease of interest in sexual activity, absence of erotic thoughts or fantasies, disinclination of initiating

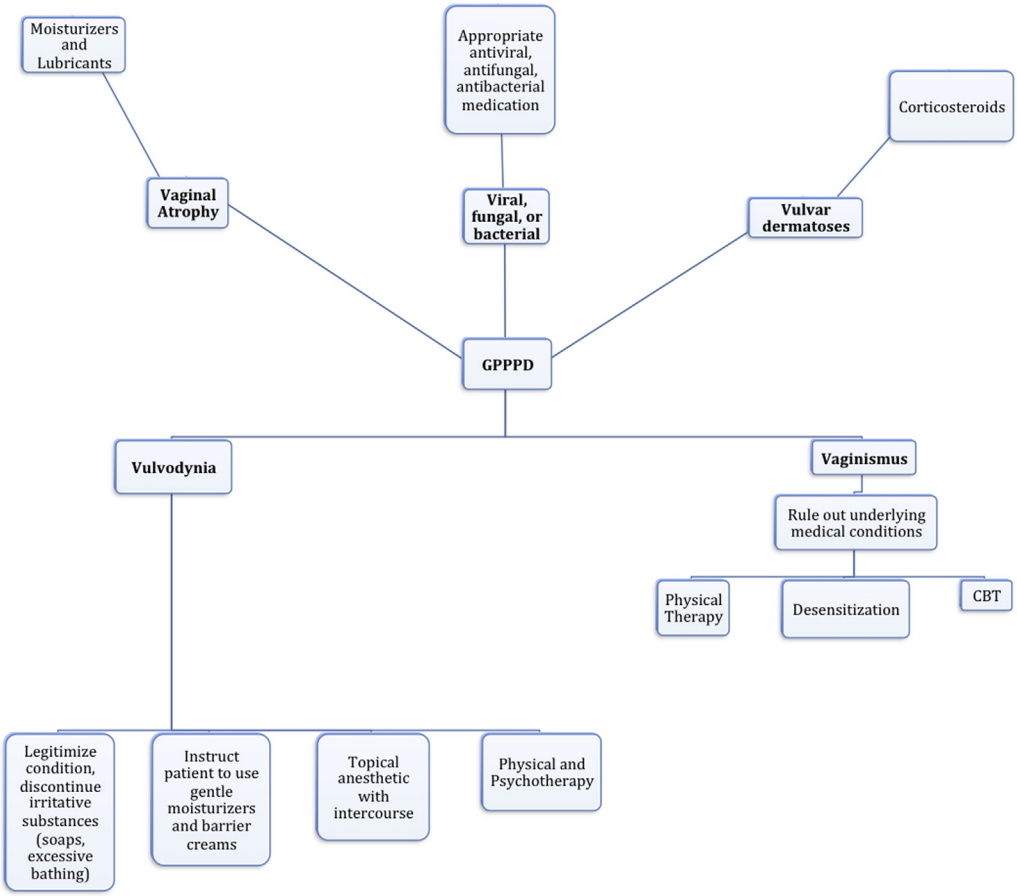

Figure 5. Management algorithm for women with GPPPD. CBT = cognitive-behavioral therapy; GPPPD = genito-pelvic pain/penetration disorder. Figure 5 is available in color at www.smr.jsexmed.org.

sexual activity with a partner, and lack of pleasure during sexual acts. The symptoms must be present for at least 6 months, they must cause significant distress to the woman, and there should be a physical cause of the disorder.[67]

To fully understand women with low sexual desire, it is important to take into account psychological and sociocultural factors. A complete assessment of the patient and her partner should include a comprehensive sexual health history including the Female Sexual Function Index questionnaire,[68] a medical history, gynecologic history, physical examination, and laboratory evaluation, if indicated. Attention to medical conditions and medications the woman is taking that might be associated with low desire should be addressed. Any psychological or psychiatric conditions of the woman or her partner including anxiety, depression, and history of abuse or trauma and relationship issues should be noted. Sociocultural factors including family issues, religious or cultural values, and financial issues warrant attention.

Table 2. Causes of infertility and sexual dysfunction in women

Sexual dysfunction	Female infertility	Infertility and sexual dysfunction
Depression	Ovulation defects	GPPPD
Medications	Premature ovarian failure	Low sexual desire and arousal disorder
Orgasmic dysfunction	Hormonal dysfunction	
Chronic illness	Tubal obstruction	
Malignancy	Endometriosis	
	Uterine/cervical causes	
	Genetic causes	
	GU or GI pathology	
	Lifestyle/environment	

GI = gastrointestinal; GPPPD = genito-pelvic pain/penetration disorder; GU = genitourinary.

Treatment interventions should begin with basic health and sex education. Gaining the trust and confidence of the woman and her partner and providing information, acknowledgement, and reassurance is important throughout the process. Goals and treatments should be discussed with the patient and her partner from the onset with an understanding that follow-up and compliance are important. Referral to a sex therapist is generally the best treatment approach. Consultation with a psychiatrist, psychologist, or internist for any other specialized medical or psychiatric conditions might be indicated. Other psychological interventions currently being used and recommended include cognitive-behavioral therapy, mindfulness meditation training, and acupuncture. Preventive health measures should be encouraged including proper diet, nutrition, weight management, and regular exercise when applicable. Providers must provide reassurance that any results will take time, patience, focus, and compliance from the two partners.

Pharmacologic interventions for female sexual desire and arousal disorder are limited and should be considered after appropriate evaluation and counseling. Bupropion, an antidepressant and mild dopamine and norepinephrine inhibitor, has been shown to have some success in the treatment of low desire.[69,70] Notably, it is a pregnancy category C drug, meaning pregnancy and lactation during treatment are not recommended. Therefore, couples must take a fertility holiday for some period if using bupropion.

Flibanserin (Addyi; Sprout Pharmaceuticals, Raleigh, NC, USA) is the newest drug approved by the Food and Drug Administration for the treatment of hypoactive sexual desire and works as a 5-HT1A receptor agonist and 5-HT2 receptor antagonist. It is important to screen and counsel patients before initiation of this drug. Use of the Decreased Sexual Desire Screener, a validated five-question survey, is a useful tool and recommended.[71] No pregnancy category has been assigned to flibanserin and no human data are available. Therefore, patients should be fully counseled and advised to use a contraceptive during treatment.

Use of androgen replacement therapy in premenopausal women with low desire has been proposed. Androgens are important in modulating female sexual response, and low levels of androgens, such as testosterone, are associated with decreased sexual desire.[72] The physiologic role of androgens in female sexual response implies that treatment with exogenous testosterone could provide benefit. Testosterone is available in many forms (topical gel, creams, implants, injection) but is entirely off-label for the treatment of sexual dysfunction, because there are no testosterone treatments for women approved by the Food and Drug Administration. Testosterone therapy has shown benefit in improving sexual function in postmenopausal women.[73] In premenopausal women, a transdermal 90-μL dose of testosterone was found to improve self-reported sexual satisfaction.[74] Although exogenous testosterone therapy for hypoactive sexual desire appears to be safe in the short and long term,[75] women should be counseled on the potential virilizing effects of testosterone before its use. Dehydroepiandrosterone also is available as an over-the-counter oral supplement. Quality assurance, dosing, and controls are variable and efficacy data have been contradictory.

Genito-Pelvic Pain/Penetration Disorders

To meet criteria for a GPPPD diagnosis, a woman must have a 6-month history of at least one of the following four symptoms: vaginal penetration difficulty, genital pain during intercourse, significant fear of pain from intercourse, and/or tensing of pelvic floor muscles during intercourse.[76] GPPPD is a broad diagnosis that includes multiple disorders that are generally divided into vulvar, vaginal, urologic, and pelvic conditions. The most notable conditions include vulvar dermatoses, inflammatory or infectious conditions, structural defects, and endometriosis. Psychological components are often present and amplified with these conditions, and patients often have concurrent sexual interest, orgasm, or arousal disorders necessitating evaluation and treatment.

There are a multitude of vulvovaginal causes of painful intercourse, with the most common in premenopausal women being localized provoked vulvodynia (LPV).[77] Light touch of the vulvar mucosa around the vaginal introitus can provoke LPV and penetration becomes painful. The cause of LPV remains unknown but is likely multifactorial and includes a chronic inflammatory condition with an initial tissue injury leading to inflammatory cytokines and neurogenic inflammation that sensitizes the area to pain.[78] Patients with LPV also frequently have pelvic floor muscle tension and concomitant anxiety or depression.[78] The underlying etiology of vulvodynia is rarely known and can cause the patient significant stress.

Management of vulvodynia should not focus on searching and treating the cause; rather, providers should simply focus on managing the patient's discomfort. Managing the patient's symptoms begins with reassuring the patient that the pain she is feeling is part of a legitimate medical condition. Women might not have a good understanding of vulvodynia and might believe it is "in their heads." Furthermore, women might be prone to excessive cleaning of the vulvar area from the belief that the symptoms are due to a hygiene issue. Frequent bathing and certain soaps can only irritate the skin and cause worsening of symptoms. Instead, women should be encouraged to use moisturizers or barrier creams to protect the area. For women with mild pain, lidocaine can be applied before penetration to provide mild anesthesia. Women also should be instructed to engage in sexual activity only during periods of high sexual arousal because the physiologic changes associated with arousal aid in preventing vulvodynia. Psychotherapy and cognitive-behavioral therapy are critical components in managing vulvodynia.[79]

Vulvar dermatoses primarily affect elderly women, although they can affect some premenopausal women. Vulvar dermatoses can manifest as lichen sclerosus or lichen planus; in these cases, the major symptoms are chronic itching, discomfort, and

scarring of the vulva. These conditions are believed to be due to autoimmune dysfunction and respond to corticosteroid therapy.[80] There are many vulvovaginal infections, and collectively they are a frequent cause of painful intercourse, particularly in young women. Herpes simplex viruses 1 and 2 cause ulcers and fissures. *Candida* species cause recurrent vulvovaginal candidiasis, which can be treated with antifungals, albeit with a high risk of relapse.

Vaginismus was previously its own diagnostic entity, but in the recent *DSM-5,* it was included under the broader diagnosis of GPPPD. Classically, vaginismus is defined as involuntary spasm of pelvic floor muscles causing painful intercourse and/or aversion to intercourse,[81] and there must be no physical cause for the symptoms. Importantly, the definition of muscle spasm is vague in relation to vaginismus, and there are no consistent electromyographic findings or demonstrations of pelvic muscle contractions in women complaining of vaginismus. In actuality, vaginismus is more likely a phobic defense mechanism to negative sexual experiences.[78] There are two main subtypes of vaginismus: primary and secondary. Primary vaginismus is when the woman has never been able to engage in penetrative intercourse, whereas secondary vaginismus is when a woman formerly could have penetrative intercourse but no longer can due to pain and muscle contraction.[82]

In the management of vaginismus, it is important to rule out any underlying physical conditions that could have triggered the pain, such as a treatable infection. Once other conditions are ruled out and vaginismus is diagnosed, a combination of physical therapy, desensitization, and cognitive-behavioral therapy might be effective.[82,83] Pelvic floor physical therapy is aimed at releasing the muscle tension in the pelvis. Next, desensitization techniques, such as Kegel exercises and self-insertion of dilators, are used. Dilators of progressively larger size are inserted by the patient into the introitus to train the woman how to voluntarily control her vaginal musculature without any associated pain. A psychosocial assessment is necessary for the patient and her partner as an integral part of the management of vaginismus.

INTEGRATED APPROACH

There is a shifting paradigm in the treatment of infertility to include psychological care.[84] According to Perelman,[85] the most effective approach to treating sexual dysfunction is a combination approach that integrates medical and psychosocial factors. Treating psychological aspects of sexual dysfunction has been shown to increase pregnancy rates in infertile couples.[86] The psychological aspect of sexual dysfunction and infertility is critical for several reasons. Of course, having any cause of infertility is a significant life stressor, as previously discussed. Beyond that, treatment of infertility alone also poses an immense challenge to a relationship; only 55% of people with fertility issues ever seek treatment[84] and 22% of people who do seek treatment discontinue in vitro fertilization attempts before completing the recommended regimen.[87] Barriers to treatment compliance have been attributed to issues in the couple (eg, relationship stress, rejecting treatment), issues with the medical management, and the clinical environment in which the couple receives treatment.[84]

An integrated approach has been proposed to address the stresses associated with treatment of infertility. The integrated strategy includes the accepted medical treatments as outlined earlier. Critically, treatment also must incorporate individual concerns of the couple that can lead to psychological stress and discontinuation of treatment. By providing the best medical options, creating a positive environment, and addressing psychological concerns of the couple, treating clinicians will provide the best care to a large group of patients in need.

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