

Ejaculatory dysfunction as a cause of infertility

Nobuyuki Kondoh

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Abstract Ejaculatory dysfunction (EjD), the most prevalent male sexual disorder, is clearly different from erectile dysfunction (ED). EjD is divided into 4 categories: premature ejaculation, delayed ejaculation, retrograde ejaculation and anejaculation. EjD-related infertility is one of the most serious problems in young patients. If sexual intercourse is achieved successfully without any ejaculate sexual partners/wives will not be able to conceive. Therefore, establishment of management of EjD as well as ED is increasingly crucial for couples wishing for a baby. The therapeutic approach of EjD-related infertility is based upon two scenarios: (1) if EjD alone is the reason for having no children, adequate treatment for EjD alone is required, or (2) if EjD is not the only reason and is combined with a worsening of semen quality, total management for male infertility (including EjD treatment) is needed. In this article, the background of EjD-related infertility is presented briefly, followed by a review of treatment modalities.

Keywords Assisted ejaculation · Ejaculation · Infertility · Medical treatment · Sperm retrieval

Introduction

Ejaculation is defined as the expulsion of seminal fluid from the urethral meatus [1]. It occurs at sexual climax, usually with orgasm. Orgasm refers to the entire response

of sexual climax—ejaculation, extragenital responses, and subjective pleasurable experience.

Ejaculatory dysfunction (EjD) is one of the major male sexual disorders and is clearly different from erectile dysfunction (ED). The spectrum of EjD extends from premature ejaculation (PE), through delayed ejaculation (DE), to a complete inability to ejaculate [anejaculation (AE)] including retrograde ejaculation (RE) [2]. Moreover, EjD which occurs in young men, can lead to low-volume ejaculate, often resulting in male infertility if they are of reproductive age.

The aim of this article is to describe the physiology and pathophysiology of EjD and briefly review the treatment methods for EjD-related infertility.

Physiology of ejaculation

Normal antegrade ejaculation consists of two main phases, emission and expulsion [3]. These two processes are mediated by afferent, efferent, somatic, sympathetic, and parasympathetic fibers. During the emission phase, the ejaculate is ejected into the posterior urethra by epithelial secretion and peristaltic contraction of the smooth muscles of the seminal tract. This phase is mediated by sympathetic nerves. Expulsion, the latter phase, occurs if the semen is rapidly advanced forward through the urethra and out the penile meatus; this involves pulsatile contractions of the bulbocavernosum and pelvic floor muscles. Furthermore, synchronized closure of the bladder neck with concomitant relaxation of the urinary sphincter is crucial to prevent the backward flow of semen into the bladder and to achieve accurate propulsion of semen [4].

The ejaculatory process integrates actions that occur in the central nervous system (CNS) and peripheral nerves.

N. Kondoh (✉)
Department of Urology, Kawanishi City Hospital,
5-21-1 Higashiuneno, Kawanishi, Hyogo 666-0195, Japan
e-mail: nmsit_k@yahoo.co.jp

Multiple neurotransmitter systems at spinal and supraspinal regions are implicated in regulation of the ejaculatory reflex. Among a wide number of neurotransmitters, including serotonin [5-hydroxytryptamine (5-HT)], dopamine, oxytocin, γ -aminobutyric acid, adrenaline, acetylcholine, and nitric oxide, 5-HT has a primary role, especially in central neurons [3, 5, 6]. Serotonergic neurons are widely distributed in the brain and spinal cord. They are predominantly found in the brainstem, raphe nuclei, and the reticular formation. The overall effect of 5-HT on ejaculation is understood to be inhibitory according to several experimental and clinical models. It is likely that the pathophysiological mechanism underpinning EjD is altered sensitivity to 5-HT or altered sensitivity to the 5-HT receptor [7]. At least 16 5-HT receptors have been identified (e.g., 5-HT1a, 5-HT1b, 5-HT2a, 5-HT2b, 5-HT2c); each of these receptors mediates different aspects of cellular activation and signaling of the 5-HT system. Activation of the presynaptic 5-HT1a receptors results in decreasing 5-HT release into the synapse through a negative feedback mechanism and reduction in ejaculatory latency [8]. Conversely, stimulation of the 5-HT2c receptor results in a delay of ejaculation in male rats. Based on these results, the hypothesis that men with PE may have hyposensitivity of 5-HT2c and/or hypersensitivity of the 5-HT1a receptor has emerged [2, 9]. Recently, dopamine (D₂)-like receptors in the CNS have been studied and concluded to be equally important to 5-HT receptors in the ejaculatory response [10].

Terminology of ejaculatory dysfunction

Any psychological disease, medical disease, or surgical procedure that interferes with central control of ejaculation or the peripheral sympathetic nerve supply to the vas and bladder neck, somatic efferent nerve supply to the pelvic floor, or somatic afferent nerve supply to the penis, can result in EjD, especially DE, AE, and anorgasmia [2]. Many reports on EjD have been published, but several terminological discrepancies, especially in the definition of the disease, have caused controversy. Some authors define AE as the total failure of seminal emission into the posterior urethra (failure of emission); however, other authors define it as complete absence of ejaculation, which includes complete RE, failure of emission, or anorgasmia. In this article, AE is defined as the latter definition because it reflects infertility-related clinical considerations better.

Premature ejaculation

PE is the most prevalent male sexual disorder. With regard to the definition of PE, three criteria should be

evaluated—short ejaculatory latency, concomitant distress, or a lack of sexual satisfaction and self-efficacy regarding the condition. The population of men with PE is not homologous, and is divided into two types, lifelong PE and acquired PE [2]. The consensus definition of lifelong PE developed by the International Society for Sexual Medicine in 2007 is ejaculation that always or nearly always occurs prior to or within about 1 min of vaginal penetration, an inability to delay ejaculation on all or nearly all vaginal penetrations, and with negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

In acquired PE, men experience ejaculations occurring too soon after a period of normal ejaculatory latencies. The onset may be sudden or gradual.

The causes may be urological disorders [11], thyroid dysfunction [12], psychological [13], or a combination of these factors. Although various epidemiological studies have shown that ~20–30% of men complain of PE [2], reliable data on the prevalence of lifelong and acquired PE in the general population is lacking.

To objectify the assessment of PE, various subjective, self-report questionnaires have been proposed. One of the most widely-used questionnaires is the Premature Ejaculation Diagnostic Tool (PEDT). Recently, PEDT was confirmed to be an extensively validated self-report measure [14]. The intravaginal ejaculatory latency time (IELT), defined as the time between the start of vaginal intromission and the start of intravaginal ejaculation, is used in clinical trials to assess the efficacy of medication for PE. A multinational study revealed that the distribution of the IELT measured with a stopwatch was positively skewed, with a median time of 5.4 min and a range of 0.55–44.1 min [15].

Delayed ejaculation

DE, also called retarded ejaculation or inhibited ejaculation, is probably the least studied male sexual dysfunction. It sometimes occurs with a reduction in the volume, force, and sensation of ejaculation. The World Health Organization 2nd Consultation on Sexual Dysfunction defines DE as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm after sufficient sexual stimulation, which causes personal distress [16]. Therefore, anorgasmia, which refers to a perceived absence of the orgasm experience independent of whether or not any or all of the physiological concomitants of ejaculation have taken place, should be included in DE.

Assessment of DE should focus on finding potential physical causes and specific psychological or acquired causes of the disorder because treatment strategies for DE

have been based upon the etiologies. Along with history-taking, physical examination may help distinguish between DE in which organic factors play a part and DE that has its roots in psychological and behavioral issues [2].

Retrograde ejaculation

RE is defined as substantial propulsion of seminal fluid from the posterior urethra into the bladder. RE can appear due to structural or functional disruption of the aforementioned ejaculation process, i.e., absence of closure of the bladder neck makes the emitted semen take the path of least resistance and flow backward into the bladder. The function of the bladder neck during ejaculation can be affected by processes altering the nerve input to the sphincter, as well as altering the neuroreceptors within the bladder neck. Hence, RE can either be partial, with some antegrade component, or complete according to the severity of neurological damage.

In the absence of antegrade ejaculation, RE is the most common cause for EjD, and accounts for 0.3–2% of male infertility [17, 18]. Moreover, the most common reason for RE in patients in infertility clinics is a history of retroperitoneal lymph node dissection (RPLND) for the treatment of testicular cancer. Other major reasons are peripheral neuropathy from diabetes mellitus, surgery (surgery of the bladder neck, transurethral resection of prostate gland), trauma, and idiopathic causes [19, 20]. The most useful assessment of RE is evaluation of post-orgasm or postcoital urine samples. A finding of >10–15 sperm per high power field confirms the presence of RE [21].

Anejaculation

In this article, AE is defined as complete absence of ejaculation. It includes complete RE, failure of emission (FE), or anorgasmia. Complete RE can be due to any of the causes of RE. FE is usually due to a neurological cause with interruption of sympathetic nerves or output. Diagnostic clues to FE are the complete absence of antegrade ejaculation combined with a non-viscous, fructose-negative, and sperm-negative post-orgasmic urinalysis [22].

Therefore, assessment of post-orgasmic urine samples is crucial to distinguish between complete RE and FE because clinical findings (including the orgasmic condition of both disorders) are not specific. ‘Idiopathic’ is used frequently if we cannot determine the accurate physiological cause of a problem, but it is also used when describing conditions that are functional. Idiopathic AE with the latter use of the word seems to reflect anorgasmia [23]. Idiopathic AE/anorgasmia is a relatively rare cause of sexual

dysfunction that usually presents as an infertility problem. If such patients have nocturnal emissions, the problem is usually considered psychogenic [24]; hence, AE/anorgasmia due to psychogenic factors should be recognized as a different pattern of DE. The other main organic change causing AE-oriented infertility is injury to the spinal cord (see below).

EjD and infertility

EjD-related infertility is one of the most serious problems in young patients. ED is an important post-testicular cause of male infertility and there have been major advances in our understanding of this disorder. However, if sexual intercourse is achieved successfully without any ejaculate sexual partners/wives will not be able to conceive. Therefore, establishment of management of EjD as well as ED is increasingly crucial for couples wishing for a baby.

Semen analysis is the most important examination for the diagnosis of male infertility. An adequate volume of ejaculate is required to carry the male gametes into the female reproductive tract, so ejaculate volume is an essential component of semen analyses [20]. If EjD affects the semen quality of infertile men, then their ejaculate volumes usually decrease or diminish; hence, ejaculate volume should be routinely investigated to detect and treat the low semen volume of EjD-related infertility. The volume measurement should be performed after 2–3 days of abstinence because semen volume increases by 11.9% per day in the first 4 days after ejaculation [25].

PE does not directly result in infertility, but co-exists in about one-third of ED patients [26]. Furthermore, PE due to hypoactive sexual desire may be a consequence of hidden hypogonadism, which leads to reduced semen quality. Chronic and frustrating PE can cause hypoactive sexual desire in both males and females, resulting in a decrease in coital frequency and consequently infertility.

DE as well as PE may occur in men who limit the sexual experience that is necessary to learn to ejaculate because of their own characteristics and sometimes due to their religious belief, especially in Western countries [27]. Such men, often having little contact with women before marriage, have low sexual desire or performance anxiety, resulting in an unconsummated marriage [28, 29] and consequent infertility.

RE and AE are common causes of EjD. The etiology and treatment of RE and AE in male infertility has been relatively well studied [19, 23]. Men who have RE or AE in their reproductive phase for whatever cause may suffer from infertility. Spinal cord injury (SCI) is the most common cause of neurogenic AE, and men with SCI who want to father children suffer from infertility because of

AE (including complete RE) rather than ED [30]. Approximately 20 years ago, only 1.8% of wives of men with SCI became pregnant. [31].

Treatment for EjD-related infertility

The therapeutic approach of EjD-related infertility is based upon two scenarios: (1) if EjD alone is the reason for having no children, adequate treatment for EjD alone is required, or (2) if EjD is not the only reason and is combined with a worsening of semen quality, total management for male infertility (including EjD treatment) is needed. In this review, the former situation is discussed briefly.

Medications

Oral pharmacotherapy is simple, least invasive, and can offer the possibility of conceiving naturally in cases of RE and AE. Different medical treatments based on increasing the sympathetic tone or decreasing parasympathetic activity have been applied as the first choice for patients with RE and AE. Among various α -adrenergic agonists or anticholinergic and antihistaminic drugs, the two agents most commonly used are imipramine and pseudoephedrine [20, 32]. For a long time, imipramine has been used for the reversal of ejaculatory disorders due to postoperative disruption of sympathetic innervations [33]. Two out of ten patients with RE after RPLND induced spontaneous pregnancy under treatment with imipramine at a daily oral dose increasing from 25 to 50 mg for 7 days before the planned ejaculation or the expected ovulation of the female partner [34]. In cases of RE in diabetic patients, treatment with imipramine, pseudoephedrine, and both drugs given together was successful in producing antegrade ejaculation by ~40, ~50 and ~60%, respectively [35]. Moreover, 3 out of 26 patients who achieved antegrade ejaculation attained spontaneous pregnancy (11.5%).

A systemic review based on the meta-analysis of articles dealing with the medical treatment of 765 patients with RE and AE revealed four major conclusions [32]. Firstly, the underlying diagnosis had no influence on the success of medical treatment. Secondly, 50% of patients with RE could induce antegrade ejaculation and 33% of patients in whom the wish for fatherhood was documented achieved a spontaneous pregnancy. Thirdly, imipramine accounted for 94% of spontaneous pregnancies achieved; therefore, imipramine (25–75 mg/day, p.o.) should be applied first in patients with RE. Lastly, the success of medical treatment of patients with non-SCI-induced AE using α -agonists is disappointing except for midodrin [36].

Reports of the medical treatment of patients with AE after SCI using α -agonists are scarce because of their poor

efficacy. In contrast, parasympathomimetic drugs (physostigmine, neostigmine) for reversal of AE are almost exclusively used [31].

Methods of assisted ejaculation

Other alternatives to pharmacotherapy in EjD patients are penile vibratory stimulation (PVS) [23, 37, 38] or electroejaculation (EEJ) [39], especially for the treatment of AE in patients with SCI.

In PVS, a vibrator is placed against the penis and mechanical stimulation is delivered to induce ejaculation. Although PVS is a relatively safe and low-cost alternative, it requires at least one intact lumbosacral spinal cord segment (above T10) [40]. EEJ may be successful in obtaining ejaculate from men with all types of SCI, including men who do not have major components of the ejaculatory reflex arc [41]. EEJ is usually performed transrectally (rectal probe EEJ). The probe is inserted in the lateral decubitus or dorsal lithotomy position. Antegrade ejaculation is captured during stimulation, and the retrograde fraction is collected via postprocedural catheterization. Almost all men (including some men with SCI) require general anesthesia for EEJ because of several side-effects mainly originating from autonomic dysreflexia.

A comparative study between PVS and EEJ showed a slight advantage in sperm quality and high patient preference in favor of PVS [42]. Therefore, PVS should be attempted first to induce ejaculation in spinal cord-injured men, with EEJ reserved for those who cannot ejaculate via PVS. In contrast, EEJ can be offered to men with other anejaculatory infertility causes such as diabetes mellitus and multiple sclerosis. According to the meta-analysis mentioned above, the prevalence of pregnancy under the treatment of infertile men with PVS and EEJ combined with various artificial methods of assisted-reproductive techniques (ART) was reported to be 47–89% and 21–78%, respectively [19].

Surgical sperm retrieval

The most common surgical procedure used for the management of EjD-related infertility is surgical sperm retrieval (SSR). This is based on the extreme progression in the techniques of ART [in vitro fertilization (IVF), intracytoplasmic sperm injection, sperm cryopreservation]. Patients with RE or AE who fail to obtain ejaculates or sufficient spermatozoa within ejaculates under non-surgical treatments could be candidates for SSR. Target sites from which sperm can be retrieved are the vas deferens [43], epididymis [44], and testis [45], as is the same with other azoospermic infertility. Vasal aspiration seems to be valuable for obtaining high motility

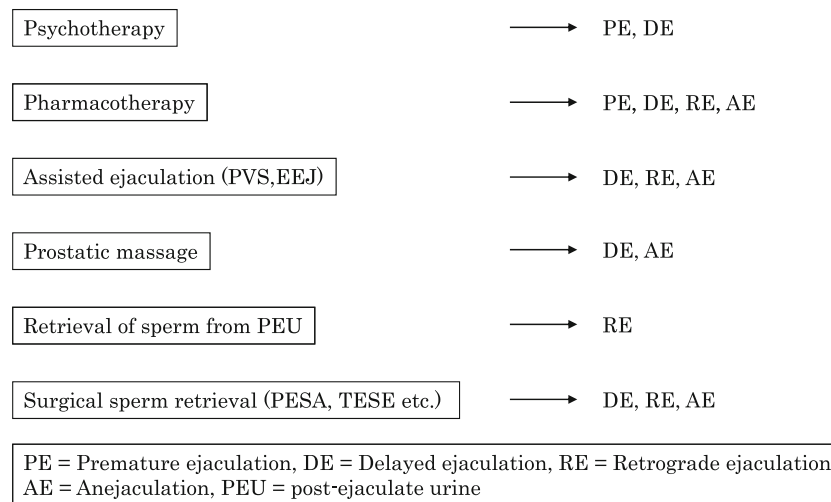


Fig. 1 Conceivable treatment modalities for EjD-related infertility and applicable EjD patterns. *AE* anejaculation, *ART* assisted-reproductive technology, *DE* delayed ejaculation, *ED* erectile dysfunction, *EEJ* electroejaculation, *EjD* ejaculatory dysfunction, *FE* failure of emission, *GABA* γ -aminobutyric acid, *5-HT* 5-hydroxytryptamine,

IELT intravaginal ejaculatory latency time, *IVF* in vitro fertilization, *NO* nitric oxide, *PE* premature ejaculation, *PVS* penile vibratory stimulation, *RE* retrograde ejaculation, *RPLND* retroperitoneal lymph node dissection, *SCI* spinal cord injury, *SSR* surgical sperm retrieval

sperm [43, 46], but live birth outcome was not significantly different among different SSR techniques in men with SCI [45]. AE is not usually associated with hypospermatogenesis as is the case in men with SCI [47], so testicular sperm extraction may be a promising SSR procedure.

Sperm retrieval can be achieved by non-surgical methods in certain situations. In men with persistent RE or if sperm within antegrade ejaculates are not sufficient for artificial insemination despite medical therapy, retrieval of retrograde ejaculates from the bladder with catheterization is possible [48]. Prostatic massage has been reported to be a simple and safe alternative method which can be offered to obtain sperm from men with idiopathic or psychogenic AE [49, 50]. Sperm obtained from nocturnal emissions in men with psychogenic AE has also been used for ART and led to a clinical pregnancy [51].

Conclusion

EjD occurring in men wishing to father children results in male infertility because of low semen volume and not supplying sufficient numbers of sperm to the female partner. Conceivable treatment methods for EjD-related infertility and the applicable ejaculatory dysfunction patterns are listed in Fig. 1. The goal of treatment is not only the achievement of improved semen volume but also the possibility of pregnancy after comprehensive investigation of male factors.

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