Review Article

The pathophysiology of acquired premature ejaculation

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Abstract: The second Ad Hoc International Society for Sexual Medicine (ISSM) Committee for the Definition of Premature Ejaculation defined acquired premature ejaculation (PE) as a male sexual dysfunction characterized by a the development of a clinically significant and bothersome reduction in ejaculation latency time in men with previous normal ejaculatory experiences, often to about 3 minutes or less, the inability to delay ejaculation on all or nearly all vaginal penetrations, and the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy. The literature contains a diverse range of biological and psychological etiological theories. Acquired PE is commonly due to sexual performance anxiety, psychological or relationship problems, erectile dysfunction (ED), and occasionally prostatitis and hyperthyroidism, consistent with the predominant organic etiology of acquired PE, men with this complaint are usually older, have a higher mean BMI and a greater incidence of comorbid disease including hypertension, sexual desire disorder, diabetes mellitus, chronic prostatitis, and ED compared to lifelong, variable and subjective PE.

Keywords: Erectile dysfunction (ED); premature ejaculation (PE); acquired premature ejaculation (acquired PE); sexual performance anxiety prostatitis

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In 1943, Shapiro (1) proposed classification of premature ejaculation (PE) into two types, types B and A. In 1989, Godpodinoff (2) renamed both types as lifelong (primary) and acquired (secondary) PE. Lifelong PE is a syndrome characterized by a cluster of core symptoms including early ejaculation at nearly every intercourse within 30–60 seconds in the majority of cases (80%) or between 1–2 minutes (20%), with every or nearly every sexual partner and from the first sexual encounters onwards (3,4). Acquired PE differs in that sufferers develop early ejaculation at some point in their life, which is often situational, having previously had normal ejaculation experiences. The main distinguishing features between presentations of these two syndromes are the time of onset of symptoms and the reduction in previously normal ejaculatory latency of acquired PE (5,6).

Community based normative intravaginal ejaculatory latency time (IELT) research and observational studies of men with PE demonstrated that although IELTs of less than 1 minute have a low prevalence of about 2.5% in the general population, a substantially higher percentage of men with normal IELT complain of PE (7-9). Waldinger and Schweitzer (10,11) explained this diversity with a new classification of PE in which four PE subtypes are distinguished on the basis of the duration of the IELT, frequency of complaints, and course in life. This classification includes natural variable PE (or variable PE) and premature-like ejaculatory dysfunction (or subjective PE) in addition to lifelong PE and acquired PE. Men with variable PE occasionally experience an early

ejaculation. It should not be regarded as a disorder, but as a natural variation of the ejaculation time in men (12). Men with subjective PE complain of PE, while actually having a normal or even extended ejaculation time (12). The complaint of PE in these men is probably related to psychological and/or cultural factors. In contrast, the consistent early ejaculations of lifelong PE suggested an underlying neurobiological functional disturbance, whereas the early ejaculation of acquired PE is more related to underlying medical causes.

Serefoglu *et al.* (13,14) confirmed the existence of these four PE subtypes in a cohort of men in Turkey. Recently, Zhang *et al.* (15) and Gao *et al.* (16) using a similar methodology confirmed similar prevalence rates of the four PE subtypes in China to that reported by Serefoglu *et al.* (13,14). This new classification and continued research into the diverse phenomenology, etiology and pathogenesis of PE is expected to provide a better understanding of the four PE subtypes (10). Although the pathogenesis of lifelong and acquired PE differs, both share the dimensions of a lack of ejaculatory control and the presence of negative personal consequences.

Definition of acquired PE

Research into the treatment and epidemiology of PE is heavily dependent on how PE is defined. The medical literature contains several univariate and multivariate operational definitions of PE (5,6,17-26). Each of these definitions characterise men with PE using all or most of the accepted dimensions of this condition: ejaculatory latency, perceived ability to control ejaculation, reduced sexual satisfaction, personal distress, partner distress and interpersonal or relationship distress. None of these defintions was supported by evidence-based clinical research.

In the last decade, substantial progress has been made in the development of evidence-based methodology for PE epidemiologic and drug treatment research using the objective IELT and subjective validated patient-reported outcome (PRO) measures. In October 2007, the International Society for Sexual Medicine (ISSM) convened an initial meeting of the first Ad Hoc ISSM Committee for the Definition of Premature Ejaculation to develop the first contemporary, evidence-based definition of lifelong PE (4). The committee was, however, unable to identify sufficient published objective data to craft an evidence-based definition of acquired PE. The committee anticipated that future studies would generate sufficient data to develop an evidence-based definition for acquired PE.

In April 2013, the ISSM convened a second Ad Hoc ISSM Committee for the Definition of Premature Ejaculation in Bangalore, India. The brief of the committee was to evaluate the current published data and attempt to develop a contemporary, evidence-based definition of acquired PE and/or a single unifying definition of both acquired and lifelong PE. Members unanimously agreed that although lifelong and acquired PE are distinct and different demographic and etiological populations, they can be jointly defined, in part, by the constructs of time from penetration to ejaculation, inability to delay ejaculation and negative personal consequences from PE. The committee agreed that the presence of these mutual constructs was sufficient justification for the development of a single unifying definition of both lifelong and acquired PE. Finally, the committee determined that the presence of a a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less was an additional key defining dimension of acquired PE.

The second Ad Hoc ISSM Committee for the Definition of Premature Ejaculation [2013] defined PE (lifelong and acquired PE) as a male sexual dysfunction characterized by:

(I) Ejaculation which always or nearly always occurs prior to or within about 1 minute of vaginal penetration (lifelong PE), or, a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE);
(II) The inability to delay ejaculation on all or nearly all vaginal penetrations;
(III) Negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy (6).

The unified ISSM definition of lifelong and acquired PE represents the first evidence-based definition for these conditions. This definition should form the basis for the office diagnosis of PE and the design of PE observational and interventional clinical trials. It is limited to men engaging in vaginal intercourse as there are few studies available on PE research in homosexual men or during other forms of sexual expression. This definition intentionally includes a degree of diagnostic conservatism and flexibility. The 1 minute IELT cut-off point for lifelong PE should not be applied in the most absolute sense, as about 10% of men seeking treatment for lifelong PE have IELTs of 1–2 minutes. The phrase, "within about 1 minute" must be interpreted as giving the clinician sufficient flexibility

to diagnose PE also in men who report an IELT as long as 90 seconds. Similarly, a degree of flexible clinical judgement is key to the recognition and interpretation of a bothersome change in ejaculatory latency with reduction of pre-morbid latency to ≤3 minutes in men with acquired PE. Men who report these ejaculatory latencies but describe adequate control and no personal negative consequences related to their rapid ejaculation do not merit the diagnosis of PE.

American Psychiatric Association has recently published *Diagnostic and Statistical Manual for Mental Disorders*, *5th edition (DSM-5)* and they defined PE as "*A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it*" (26). This must have been present for at least 6 months and must be experienced on almost all or all (approximately 75–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts). In addition, it causes clinically significant distress in the individual and it is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition". Although the DSM-5 definition classifies PE as "lifelong" and "acquired", it does not provide different cut-off IELT values for these conditions. However, the DSM-5 categorizes PE according to the IELT values as follows: (I) mild PE, ejaculation occurs within approximately 30 seconds to 1 minute of vaginal penetration; (II) moderate PE, ejaculation occurs within approximately 15–30 seconds of vaginal penetration, and; (III) severe PE, ejaculation occurs prior to sexual activity, at the start of sexual activity, or within approximately 15 seconds of vaginal penetration.

Prevalence of acquired PE

Reliable information on the prevalence of lifelong and acquired PE in the general male population is lacking. PE has been estimated to occur in 4–39% of men in the general community (27-33), and is often reported as the most common self reported male sexual disorder (34). There is, however, a substantial disparity between the incidence of PE in epidemiological studies which rely upon either patient self-report of PE and/or inconsistent and poorly validated definitions of PE (9,32,35), and that suggested by community based stopwatch studies of the intravaginal ejaculation latency time (IELT), the time interval between penetration and ejaculation (8). The latter demonstrates that the distribution of the IELT is positively skewed, with a median IELT of 5.4 minutes (range, 0.55–44.1 minutes), decreases with age and varies between countries, and supports the notion that IELTs of less than 1 minute are statistically abnormal compared to men in the general western population (8).

Prevalence data derived from patient self report will be appreciably higher than prevalence estimates based on clinician diagnosis utilizing the more conservative ISSM definition of PE. The following studies demonstrate the varying prevalence estimates ranging from 30% down to 3%. Data from The Global Study of Sexual Attitudes and Behaviors (GSSAB), an international survey investigating the attitudes, behaviors, beliefs, and sexual satisfaction of 27,500 men and women aged 40–80 years, reported the global prevalence of PE (based on subject self-report) to be approximately 30% across all age groups (36,37). Perception of "normal" ejaculatory latency varied by country and differed when assessed either by the patient or their partner (38). A core limitation of the GSSAB survey stems from the fact that the youngest participants were aged 40 years, an age when the incidence of PE might be different from younger males (34). Contrary to the GSSAB study, the Premature Ejaculation Prevalence and Attitude Survey found the prevalence of PE among men aged 18 to 70 to be 22.7% (33). The real prevalence of PE is difficult to assess in clinical practice (34).

Basile Fasolo *et al.* reported that 2,658 of 12,558 men (21.2%) attending a free andrological consultation self-diagnosed PE, the majority describing acquired PE (14.8%) with 4.5% describing lifelong PE (39). In contrast, Serefoglu *et al.* (13) reported that the majority of PE treatment-seeking patients described lifelong PE (62.5%) compared to acquired PE (16.1%). Similar findings were reported by Zhang *et al.* who found that the majority of 1,988 Chinese outpatients described lifelong PE (35.6%) or acquired PE (28.07%). These data provide evidence that lifelong and acquired PE patients comprise the majority of the patients who seek treatment for the complaint of ejaculating prematurely. In addition, there appears to be a disparity between the incidence of the various PE sub-types in the general community and in men actively seeking treatment for PE.

Consistent with this notion, Serefoglu *et al.* (14) subsequently reported an overall PE prevalence of 19.8% comprising lifelong PE (2.3%), acquired PE (3.9%), variable PE (8.5%) and subjective PE (5.1%). Using similar research methodology, Gao *et al.* (16) reported that 25.80% of 3,016 Chinese men complained of PE, with

Table 1 Risk factors for acquired premature ejaculation (PE)

Risk factors	Diseases
Psychorelational	Anxiety, relational and marital problems
Endocrine	Hyperthyroidism
Urologic	Prostate inflammation/infection
Other sexual symptoms	Comorbid with erectile dysfunction (ED), hypoactive sexual desire, female sexual dysfunction

similar prevalence of lifelong PE (3.18%), acquired PE (4.84%), variable PE (11.38%) and subjective PE (6.4%). Of particular interest is the report of Serefoglu *et al.* (14) that men with acquired PE are more likely to seek medical treatment than men with lifelong PE (26.53% *vs.* 12.77%). This finding was confirmed by Gao *et al.* who demonstrated that acquired PE patients were more likely to seek (17.12% *vs.* 14.58%) and plan to seek (36.30% *vs.* 27.08%) treatment for their complaints compared to men with lifelong PE (16). These data suggest that the prevalence of acquired PE in the community is approximately around 4% among sexually active adults and that these patients are more likely to seek medical treatment.

Aetiology of acquired PE

Historically, attempts to explain the etiology of PE have included a diverse range of biological and psychological theories. Most of these proposed aetiologies are not evidence based and are speculative at best. Although men with lifelong and acquired PE appear to share the dimensions of short ejaculatory latency, reduced or absent perceived ejaculatory control and the presence of negative personal consequences from PE, they remain distinct and different demographic and etiological populations (40).

Acquired PE is commonly due to sexual performance anxiety (41), psychological or relationship problems (41), erectile dysfunction (ED) (36), and occasionally prostatitis (42), hyperthyroidism (43), or during withdrawal/detoxification from prescribed (44) or recreational drugs (45). Consistent with the predominant organic etiology of acquired PE, men with this complaint are usually older, have a higher mean BMI and a greater incidence of comorbid disease including hypertension, sexual desire disorder, diabetes mellitus, chronic prostatitis, and ED compared to lifelong, variable and subjective PE (13-16,39,40,46).

As such, A-PE is best regarded as a psychoneureoendocrine and urological symptom with possible comorbidity with ED and other sexual disturbances. The manifold candidate aetiologies of A-PE are perhaps best regarded as a series of psychological, relational and organic risk factors for A-PE (*Table 1*).

Psychological risk factor

Psychological problems such as sexual performance anxiety, psychological or relationship problems may cause acquired PE (41).

Anxiety has been reported as a cause of PE by multiple authors and is entrenched in the folklore of sexual medicine as the most likely cause of PE despite scant empirical research evidence to support any causal role (47-49). It should be noted however that anxiety and depression may also be the effect rather than the cause of PE and several recent studies have confirmed the bi-directional relatiopnship between anxiety, depression and PE (50-54).

Several authors have suggested that anxiety activates the sympathetic nervous system and reduces the ejaculatory threshold as a result of an earlier emission phase of ejaculation (48). The possibility that high levels of anxiety and excessive and controlling concerns about sexual performance and potential sexual failure might distract a man from monitoring his level of arousal and recognising the prodromal sensations that precede ejaculatory inevitability has been suggested as a possible cause of PE by several authors (55-58). The association between PE, anxiety and other psychological disorders has been measured by the Hospital Anxiety and Depression Scale (HADS) (59). Furthermore, anxiety appears to interact with and exacebrate the somatic and perhaps genetic vulnerability to rapid ejaculation of some men (60).

The causal link between anxiety and PE has been largely regarded as speculative and not supported by any empirical evidence and is in fact contrary to empirical evidence from other researchers. Strassberg *et al.* [1990] failed to demonstrate any difference in sexual anxiety between a control group of men with normal ejaculatory control and men with PE (60). However, Corona *et al.*

elegantly demonstrated high levels of free floating anxiety in A-PE (61). Consistent with this finding, Rajkumar *et al.* reported that performance anxiety during intercourse was significantly associated with acquired PE (52). In addition, men with pre-existing anxiety disorders were more likely to experience performance anxiety related to sex, and to have PE without comorbid ED (51). Furthermore, men with subjective PE and a normal ejaculatory latency appear to have a greater psychological burden than men with definition diagnosed PE including depression, low self-esteem, bother, and low sexual satisfaction (54). However, PE appears to be less associated with trait anxiety and depression compared to ED, a finding that corroborates the recent acknowledgement of PE as a more biologically based condition (50).

Sexual behaviour such as PE can also be adversely effected by several other psychological problems and confounding factors. PE has been considered frequent, if not normal, during early sexual experiences. Masters and Johnson suggested that confounding factors such as the risk of unwanted discovery (such as copulating in a car), experiences with prostitutes, and anxiety due to poor sexual education (e.g., absence of adequate knowledge of contraceptive methods) might worsen the poor ejacultory control commonly observed in young men (62). Social phobia can be a tract characterizing both lifelong PE and acquired PE. PE was the most common sexual dysfunction in male social phobic patients (63). PE was highly associated (P=0.015) with social phobia, with an odds ratio of 2.55 (64). Sexual disorders can be the result of distortions of belief and false convictions about sexuality which are established in childhood. Destructive attitudes are usually exerted by parents but also by other power figures within and outside the family (65). Classic psychoanalytic theories have identified varying degrees of sadistic or narcissistic behavior in sufferers of PE (66). Some psychoanalysists identify men who ejaculate prematurely as typically passive and masochistic in their marriage and obsessive-compulsive in character (67). These theories were the basis of Helen Kaplan's initial premise that PE is the result of an unconscious hatred of women (56,68). By ejaculating quickly, a man symbolically and physically "steals" the woman's orgasm. However, the same researcher rejected her own theory when she found that men with PE do not have any particular neuroses or personality disorders (56).

Alexithymia is a deficit in identifying and communicating emotions that is presumed to play an important role in psychosomatic diseases. Alexithymic features, and in particular, an externally oriented cognitive style, can be seen as possible risk and/or maintenance factors for PE. Alexithymia could represent a variable to be assessed for an integrated diagnosis and treatment of PE (69).

In conclusion, the etiological approach of psychology to PE in general and to A-PE in particular should be re-thought. Psychological involvement can be either a cause or caused by A-PE.

The sexual dysfunction risk factor

Multiples studies have observed that hypoactive sexual desire, ED, partner female sexual dysfunction (FSD) and PE often coexist (33,36,70-74) (*Table 2*). Recent data demonstrates that as many as half of subjects with ED also experience PE (33,36,39).

Hypoactive sexual desire may also lead to PE, due to an unconscious desire to abbreviate unwanted penetration (77). Similarly, diminished sexual desire can be a consequence of chronic and frustrating PE. Interesting, low sexual desire may be due to a lack of sexual arousal, such as in ED. PE and low desire, singly or in combination, are, in fact, significantly associated with severe rather than mild ED at presentation (76). Furthermore, FSD including anorgasmia, hypoactive sexual desire, sexual aversion, sexual arousal disorders, and sexual pain disorders such as vaginismus (74) may also be related to acquired PE. Female sexual dysfunction may be secondary to the male PE with or without ED, and can be considered as a frequent complication of this condition. In other cases, PE may be the result of hidden female arousal difficulties (78). Such partner influences emphasize the need to diagnose and treat the couple, not simply the patient (79).

Several large cross sectional observational studies confirm the link between ED and PE (*Table 2*) (33,36,39,72,75,76). The Premature Ejaculation Prevalence and Attitudes (PEPA) Survey of 12,133 men from three countries found self-reported ED rates of 31.9% and 11.8% in men with and without PE respectively (33). Basile Fasolo *et al.* reported that ED is more common in men with PE, particularly in men with acquired PE (39). The GSSAB found that men with PE had a country specific odds ratio of 3.7–11.9 of having ED (36). In a nationally representative sample of 1,475 Swedish men, 23% of men reporting erectile difficulties also reported PE (75).

While these large cross-sectional studies clearly establish the frequent coexistence of the two conditions, they do not provide information about temporality and consequently

Table 2 Co-existence of ED and PE

Author	n	PE definition	ED definition	Findings
Porst (33)	12,133 internet survey	Self-reported low/absent control over ejaculation that bothered the respondent and/or the sexual partner	Self-reported	ED prevalence: in men with PE =31.9%; in men without PE =11.8%
Fugl-Meyer (75)	1,475 community-based survey	Self-reported ejaculation shortly after penetration	Self-reported	PE in 23% of patients with ED
Corona (72)	882 sexual health clinic	Reported IELT <1 minute	SIEDY	20.9% had ED and PE; 5% had only PE
Basile Fasolo (39)	12,558 urology/ andrology clinic	Self-reported, as per DSM-IV	Self-reported dissatisfaction with erections	OR for ED: lifelong PE: 2.5; acquired PE: 9.6
el-Sakka (76)	1,680 ED clinic	Lack of control with ejaculation shortly after penetration	EFD-IIEF	PE prevalence: overall: 45%; in men with mild ED: 29%; in men with severe ED: 52%

ED, erectile dysfunction; PE, premature ejaculation; IELT, intravaginal ejaculatory latency time; SIEDY, structured interview on erectile dysfunction; EFD-IIEF, erectile function domain of the international index of erectile function.

causality.

In a cohort of 184 men attending a sexual dysfunction clinic, 121 complained of ED, 52 of PE, and 11 of both conditions (24). Interestingly, careful evaluation and administration of the IIEF-5 demonstrated that 24% of patients only complaining of ED actually had experienced PE prior to ED onset. Moreover, antecedent or concurrent ED was identified by the IIEF-5 in 40% of patients complaining of PE only. Patients with ED and PE were initially treated with a type 5 phosphodiesterase (PDE5) inhibitor alone, which resulted in partial or complete resolution of PE in 30%.

Jannini *et al.* reported a bidirectional relationship between ED and PE where either one can cause/exacerbate the other, potentially creating a vicious cycle (24). Subjects with ED may either require higher levels of stimulation to achieve an erection or intentionally "rush" intercourse to prevent early detumescence of a partial erection, resulting in ejaculation with a brief latency (24). On the other hand, PE can result in ED. Conscious efforts to delay ejaculation by reducing the level of excitation might result in loss of penile erection. Interestingly, various studies have demonstrated that the prevalence of PE is positively associated with ED severity (61,76,80). el-Sakka *et al.* reported that PE was present in 29.5% of men with mild ED, and 52.4% those with severe ED (76). In addition, high levels of performance anxiety related to ED may serve to only worsen their prematurity. A study of more than 800 men attending an outpatient clinic for sexual problems found that anxiety symptoms, as assessed by a validated questionnaire, were significantly associated with erectile difficulties and PE (81).

Endocrine risk factors

Hormones play a central role in the control of ejaculation (82); this implies that pathological hormonal levels may directly or indirectly affect the ejaculatory control (83).

The role of sex steroids

Low serum testosterone levels have been inconsistently associated with PE (84,85). However, other reports have suggested that hypogonadism can be considered a possible cause of delayed ejaculation (86,87). Testosterone plays a crucial role in male sexual response, acting at both the central and peripheral levels, and is a clear determinant of motivation to seek sexual contact.

Several studies in hypogonadal men have demonstrated that testosterone replacement has an unequivocal role in restoring sexual desire, spontaneous sexual thoughts and attraction to erotic stimuli. The testosterone-dependency of PDE5 expression and activity has also been demonstrated in other portions of the male genital tract such as the vas deferens, a critical effector for semen emission and

ejaculation (88,89). Recent data suggests that testosterone plays a facilitatory role in the control of ejaculatory reflex (87). However, Paduch *et al.* reported that testosterone replacement was not associated with significant improvement in ED in androgen-deficient men (90). Different testosterone levels identify different subsets of ejaculatory disturbance. While a higher testosterone level may characterize PE, delayed ejaculation is associated with hypogonadal levels. Taken together, these data suggest a role for androgens in the mechanism of ejaculation (87).

Both central and peripheral mechanisms have been advocated to explain this association. The first explanation is psychoendocrinal. Testosterone level, in addition to its action on sexual response, profoundly influences male behaviour. High testosterone levels in human adults are associated with leadership, toughness, personal power and aggressive dominance (91). Rowland considers delayed ejaculation to be essentially characterized by the uncoupling of a decreased subjective and a preserved genital reaction in sexual arousal (92). It could thus be speculated that hypogonadism and related reduction in sexual confidence and aggressiveness could play a critical role in the control of ejaculation timing, reducing the internal cues for reaching orgasm and ejaculation. The second hypothesis is neurological. Recent data from animal models seem to support the central action of testosterone in the control of the ejaculation reflex. Keleta *et al.* (93) demonstrated that long-term testosterone treatment in rats significantly decreased 5-HT in the brain. Another intriguing possibility involves the possible peripheral role of testosterone in regulating male genital tract motility. In rabbit hypogonadism, it was found that PDE5 is less expressed and biologically active in the vas deferens (89). Testosterone administration completely reversed these alterations. Hence, it is possible that hypogonadism-associated delayed ejaculation is due to an increased inhibitory nitrergic tone on male genital tract smooth muscle cells. A "mechanical" mechanism of testosterone action in ejaculation control can also be possible. A hypogonadism-induced reduction in semen volume may perturb the dynamics of the seminal bolus propulsion, possibly explaining ejaculation difficulties in some subjects. In fact, low testosterone directly reduces ejaculate volume, which may result in a lack of stimulation of accessory glands such as the prostate and seminal vesicles, which are well-known androgen targets. Finally, it cannot be excluded that the testosterone differences demonstrated are the consequences of sexual disturbances mirroring differences in sexual behaviour, such as copulation frequency (94).

In conclusion, several possible mechanisms may connect androgen levels with the complex machinery of ejaculation. Clinical studies are currently in progress to further establish the role of testosterone in ejaculatory dysfunction.

The role of prolactin

In a consecutive series of 2,531 patients interviewed using structured interview on erectile dysfunction (SIEDY) (a 13-item tool for the assessment of ED-related morbidities) (95), and Middlesex Hospital Questionnaire (96), for the evaluation of psychological symptoms, low prolactin levels are associated with PE and anxiety symptoms (97). Hypoprolactinaemia may be a consequence rather than a cause of PE. In fact, many psychological disturbances such as stress and frustration for chronic or acquired inability to enjoy sex can provoke a central serotoninergic neuroendocrine imbalance seen in the relative hypoprolactinemia found in patients with PE.

The role of thyroid hormones

The impact of thyroid hyper- and hypofunction in male sexual function has been studied only very recently. This is probably the consequence of: (I) the apparently low clinical significance given to male sexual symptoms in comparison with the systemic effects of thyroid hormone excess and defect; (II) the paucity of clinical studies, as thyroid disease is less common in men; (III) the embarrassment of patients and physicians when discussing sexual dysfunction in the "traditional" setting of the endocrine outpatient clinic (98). However, it has been found a high prevalence of acquired PE in hyperthyroid patients, whereas in hypothyroid subjects the main sexual complaint was delayed ejaculation (43,61). Both ejaculatory dysfunctions reverted on achievement of euthyroidism in the absence of any other treatment for the sexual symptom. Interestingly, suppressed levels of TSH as a marker of hyperthyroidism have been demonstrated in acquired PE (61) but, obviously, not in patients with lifelong PE (99). All these data suggest a direct involvement of thyroid hormones on the physiology of ejaculation.

As the relationship between thyroid hormones and ejaculatory mechanisms is currently unknown, three possible sites of action have been suggested: the sympathetic nervous system, the serotoninergic pathway and the endocrine/paracrine system (100-102). Most manifestations of thyrotoxicosis and sympathetic nervous system activation overlap. This may suggest a similar action

on ejaculation, a reflex largely dependent on sympathetic and parasympathetic tone. However, plasma catecholamines and their urinary metabolites are usually normal in hyperthyroidism (100). On the other hand, some studies have found that thyroid hormones augment sensitivity to adrenergic agonists by increasing adrenoceptor density and Gs/Gi protein ratio through an over-activation of adenylate cyclase (101). This leads to increased sympathetic activity with normal circulating catecholamine levels. In hyperthyroid patients, the increased adrenergic tone may trigger both premature and delayed ejaculation, either acting directly on smooth muscle contractility/relaxation or indirectly on anxiety and irritability. The opposite may occur in hypothyroid patients (102). Considering the neuropsychological reactions to thyroid hormone excess (hyperkinesia, nervousness, anxiety, emotional lability), PE may be also a non-specific disease-related complaint, disappearing when a euthyroid state is achieved. However, in light of the widespread distribution of thyroid hormone nuclear receptors within the brain, it can be hypothesized that iodothyronines specifically alter the central serotoninergic pathway (103), leading to diminished ejaculation control. In animals with experimentally-induced hypothyroid states, increased serotonin turnover in the brainstem is consistently reported (104) and thyroid hormone replacement is associated with increased cortical serotonin concentrations and augmentation of serotonergic neurotransmission by desensitization of the serotonin inhibitory 5-HT1A (auto-inhibition) (104). Finally, delayed ejaculation is a common and therapeutically useful side effect of serotoninergic drugs, indicating that this pathway is fundamental for ejaculatory control.

Another way that thyroid hormones may affect the ejaculatory mechanism could be through oestrogen metabolism. Hyperthyroidism increases levels of sex hormone binding globulin (SHBG), which binds androgens with higher affinity than oestrogens, leading to a relative hyperoestrogenism (105). It has been demonstrated in hypogonadic rabbits that oestrogens, but not androgens, fully restore oxytocin-induced epididymal contractility, up-regulating oxytocin receptor gene and protein expression, and that deprivation of endogenous oestrogens induces oxytocin hypo-responsiveness (106,107). As oxytocin is closely involved in the ejaculatory mechanism (108) both centrally (109) and peripherally (110), this may account for the close correlation between hyperthyroidism and PE. As an ancillary possibility, thyroid hormone receptors have been described in the animal (111) and human testis (112), and may also be present in other male genital tract structures, triggering ejaculation. Finally, although excluded in the original report (43), some cases of PE in hyperthyroidism are comorbid with ED, which may in turn exacerbate the loss of ejaculatory control (24).

PE and hyperthyroidism

The majority of patients with thyroid hormone disorders experience sexual dysfunction. Studies suggest a significant correlation between PE and suppressed TSH values in a selected population of andrological and sexological patients. The 50% prevalence of PE in men with hyperthyroidism fell to 15% after treatment with thyroid hormone normalization (43). Although occult thyroid disease has been reported in the elderly hospitalized population, it is uncommon in the population who present for treatment of PE and routine TSH screening is not indicated unless clinically indicated (113).

Urologic risk factors

PE and chronic prostatitis

Acute and chronic prostatitis, prostatodynia, or chronic pelvic pain syndrome (CPPS) is associated with ED, PE and painful ejaculation (114-118). This syndrome includes urogenital pain, ejaculatory pain, urinary dysfunction, and sexual dysfunction. In the literature, CP has been closely linked with PE (42,117-120). While the co-existence of these conditions is common, a true causal relationship or mechanism has not been established. Prevalence and treatment studies are the cornerstone of this relationship and this data has given researchers insight into potential diagnostic and treatment options for men with PE. The relationship between chronic prostatitis, CPPS and PE is supported by several recently published studies which focus more on epidemiology and largely ignore treatment. Most of these have are limited by poor study design including inconsistent or absent methodologies of microbiological diagnosis of prostatitis and the lack of a validated questionnaire for combined evaluation of chronic prostatitis and sexual dysfunction.

Painful ejaculation is a common symptom of chronic prostatitis or CPPS and is included in all prostatitis symptom scores. In 3,700 men with benign prostatic hypertrophy (BPH), painful ejaculation was reported by 18.6% and was associated with more severe lower urinary tract symptoms

(LUTS), and a 72% and 75% incidence of ED and PE respectively (121). Several studies report PE as the main sexual disorder symptom in men with chronic prostatitis or CPPS with a prevalence of 26–77% (119,122-125).

Prostatic inflammation and chronic bacterial prostatitis have been reported as common findings in men with both lifelong and acquired PE (42,120,126). Shamloul and el-Nashaar reported prostatic inflammation and chronic bacterial prostatitis in 64% and 52% of men with PE (120). The 41.4% incidence of prostatic inflammation in men with lifelong PE parallels that reported by Screponi (42), but is inconsistent with the proposed genetic basis of lifelong PE, and assumes the presence of prostatic inflammation from the first sexual experience. Although physical and microbiological examination of the prostate in men with painful ejaculation or LUTS is mandatory, there is insufficient evidence to support routine screening of men with PE for chronic prostatitis. The exact pathophysiology of the link between chronic prostatitis, ED and PE is unknown. It has been hypothesised that prostatic inflammation may result in altered sensation and modulation of the ejaculatory reflex but evidence is lacking (120).

Liang *et al.* continued to evaluate this association with a study of 1,768 Chinese men with CP and observed that overall sexual dysfunction was present in 49% of this cohort whereas PE, in particular, was present in 26.2% of these patients (119). Duration of CP was shown to be a contributing factor in sexual dysfunctions (PE and ED), where stratification of duration of CP revealed that individuals with ≥19 months of CP-like symptoms have a greater prevalence of PE (44.2%) than those with less than 19 months (24.4%).

In a follow-up study, 7,372 Chinese men were evaluated via cross-sectional survey to determine the correlation between PE and CP and study results demonstrated 15.3% of randomly recruited Chinese men self-reported PE (127). In addition, of those that reported PE, 64.1% reported prostatitis-like symptoms determined by criteria developed by Nickel *et al.* (128). Men with clinical symptoms of CP suffered from PE at a rate of 36.9%, higher than the general population.

In comparison, a study by Gonen *et al.* evaluated 66 CP patients and found a PE rate of 77.3%. In comparison, ED was only associated with PE in 15.2% of these patients (123). A similar study evaluated 43 patients with type III prostatitis and found a significant difference between PE prevalence in these patients (67.44%) *vs.* their control group (40%) (129). An Italian study also evaluated 399 patients with symptoms that were suggestive of CP to determine prevalence of sexual dysfunction within this cohort (125). The authors demonstrated that, 220 (55%) of the patients had ejaculatory dysfunctions, with 110 (28%) of these patients reporting PE. The authors also showed that PE was more frequently associated in patients with high to medium levels of inflammation compared to patients with lower levels of inflammation. This analysis was consistent with Shamloul's study as noted previously (120). In addition, these researchers stratified prevalence of PE by NIDDK/NIH classification of prostatitis. PE was evenly associated throughout category II (33%), IIIa (29%), and IIIb (21%), respectively (P=0.125).

Several studies have also shown that antibiotic treatment of patients with CP may help to delay ejaculation. Treatment for CP is usually targeted towards gram-negative rods, but other common species may arise, such as *Enterococci*, *Ureaplasma urealyticum*, *and Pseudomonas species* (120,130). The initial account that showed improvement in ejaculatory function through treatment of CP was a study by Boneff (131). Patients were treated with a topical hydrocortisone-antibiotic mixture introduced into the posterior urethra via catheterization after prostate massage. The men who underwent this treatment (n=42) experienced a 52% improvement in ejaculation status, defined by prolongation of copulation for up to 5 minutes. There was a greater benefit from this treatment in patients with co-existing CP (15/22, 68.2%) than just PE alone (7/20, 35%). In a follow-up to their previous prevalence study, El-Nashaar and Shamloul studied a cohort of 145 men who complained of PE for at least 6 months prior to the study (132). Expressed prostate secretion (EPS) positive prostatitis was found in 94 (64.8%) of these men, all of who were asymptomatic antibiotic treatment was given for 1 month and 62 (83.9% of those treated) showed a significant increase in their IELT and no recurrence of PE or CP after 4 months. Zohdy *et al.* performed a similar study of 210 men with CP symptoms and concomitant PE (133). The goal was to determine clinical parameters that may predict successful outcomes in treatment of CP. They found that 59.0% of the men treated with antimicrobial therapy had a significantly greater increase in IELT, in comparison to an untreated cohort. In addition, there was a difference in outcome between men with acquired PE and lifelong PE, where men with acquired PE responded more effectively to the antibiotic treatment. They also found that men with higher levels of inflammation experienced greater benefits (70.0%) to antibiotic treatment in their IELTs compared to individuals with lower levels (31.4%).

In summary, the urologic literature has shown a higher prevalence of CP or CPPS among PE patients and vice versa. There is also an association between the dimensions of the patient's CP, i.e., duration of symptoms and levels of inflammation, and the possibility of having PE. Lastly, the beneficial effect of treatment with antibiotics on the improvement of ejaculatory function has been strongly supported.

Together, this evidence strongly supports the idea that CP may be a common cause of both acquired and lifelong PE, thus it should be ruled out, especially in men with associated pelvic pain and/or urinary symptoms. EPS analysis, such as the Meares-Stamey test, is a cheap and easy tool that can delineate such an etiology of the patients with PE (134). Culture of the EPS with speciation of the organism may be beneficial in cases refractory to empiric antibiotic use. Although the connection between prostatic inflammation and pathology of the ejaculatory reflex has been proposed to occur through modulation of the neurophysiologic pathway (135), further studies are required to elucidate the exact mechanism.

Varicocele and PE

Varicocele, the abnormal dilatation of veins in the pampiniform plexus due to retrograde venous flow, has been shown to impact sexual function. Varicoceles are a common urological condition, with the estimated incidence ranging from 15% of the general population to 35% of men with primary fertility issues depending on the screening method (136).

The impact of varicocele on ejaculation has recently been hypothesized as a possible etiology of acquired PE. In an Italian cross-sectional study, Lotti *et al.* evaluated 2,448 sexual dysfunction patients for the presence of varicocele (137). Their comparison of groups, varicocele *vs.* no varicocele, showed a significant difference in PE status (29.2% *vs.* 24.9% in subjects with or without varicocele, respectively), when adjusted for factors such as age, anxiety levels, and prolactin levels. The researchers showed an association between severity of varicocele on Doppler ultrasound analysis and seminal levels of interleukin-8, a surrogate marker for non-bacterial prostatitis. These findings were extrapolated to hypothesize that PE may be a clinical symptom of an underlying inflammatory state caused by varicocele and/or prostatitis. The authors also note that venous congestion through a connection between the testicular and prostatic venous systems may predispose a varicocele patient to prostatitis. Consistent with these findings, there have been preliminary reports from methodologically flawed studies of improvements in men with PE treated with varicoelectomy (138,139).

In conclusion, the presence of varicocele has been shown to be associated with high levels of inflammation in the pelvic area. In the large study conducted by Lotti *et al.*, biological support was given to show the association between the PE and varicocele, yet it is unsure which of these states may predispose a man to the other pathology. More research should be conducted to understand the underlying mechanism that connects these two pathologies.

Circumcision and PE

Circumcision, removal of the penile foreskin, is a routine practice among Islamic and Jewish communities. Considering the loss of high amount of specialized sensory mucosa during this surgery, some authors claimed that circumcision has a negative impact on the overall sensory mechanism of the human penis (140). Some international epidemiologic studies demonstrated lower prevalence for PE in Middle East, confirming this presumption (36). However, clinical studies regarding the penile sensitivity, PE status and sexual satisfaction report conflicting results are not conclusive (11,141-145).

Fink *et al.* found that adult circumcision was associated with worsened erectile function, decreased penile sensitivity and improved satisfaction without causing any changes in sexual activity (141). Waldinger *et al.* measured the IELTs of 500 men in the Netherlands, United Kingdom, Spain, the United States and Turkey. They observed that Turkish men, who all but two were circumcised (122/124), had significantly lower median IELT (3.7 minutes) compared to the median IELT value of each of other countries (11). Interestingly, the authors also compared circumcised men with not-circumcised men in countries excluding Turkey and observed that IELT values were independent of circumcision status, which has been also confirmed with a latter study (7).

Senkul *et al.* evaluated the sexual performance of 42 adults before and 12 weeks after circumcision by using Brief Male Sexual Function Inventory (BMSFI) questionnaire and could not demonstrate any difference in sexual function (143). Similarly, recent studies have investigated the role of postcircumcision mucosal cuff length in PE by measuring it in men with and without PE (115,146,147). These authors concluded that neither post-circumcision mucosal cuff length nor circumcision timing is a risk factor for PE. Furthermore, the

notion that circumcision might alter penile skin sensitivity and affect sexual function was largely de-bunked by Malkoc *et al.* who demonstrated that the density of fine nerve endings in the foreskin of circumcised men with PE was not different from that of circumcised non-PE controls (148). Of interest is the report of Alp *et al.* that not only did circumcision during adulthood not adversely affects ejaculatory function but was associated with significantly longer mean IELTs after circumcision (144). Similarly, Gao *et al.* reported that adult circumcised men experienced significantly improved IELT, control over ejaculation, and satisfaction with sexual intercourse compared to a control group (P<0.001 for all) (145).

A lack of any relationship between circumcision and risk of PE was confirmed in two extensive systematic analyses of reported data (149,150).

Idiopathic A-PE

The percentage of patients having PE of unknown cause is currently not available. It was frequent in the recent past to consider these patients as psychogenic. However, this is not correct and the term psychogenic should be substituted with that of "idiopathic" PE (151). Future research will provide new pathophysiological elements and the number of subjects with idiopathic PE—probably the majority at the moment—will decrease progressively.

Conclusions

Recent epidemiological and observational research has provided new insights into PE and the associated negative psychosocial effects of this dysfunction. The recently developed multivariate evidence-based ISSM definition of lifelong and acquired PE provides the clinician a more discriminating diagnostic tool and should form the basis of the office diagnosis of lifelong PE.

Although there is insufficient empirical evidence to unequivocally identify the aetiology of PE, there is limited evidence to suggest that acquired PE is most often due to sexual performance anxiety, psychological or relationship problems and/or ED and to a lesser extent, chronic prostatitis, CPPS or hyperthyroidism. Although the absence or deficiency of control in ejaculation is the most common sexual symptom (34), acquired PE remains under-diagnosed and under-treated, despite the fact that it can be successfully treated (152). However, increased medical awareness, careful diagnosis and sub-typing, recognition of the pathogenetic mechanism in individual patients and the forthcoming availability of new drugs specifically designed for PE will give the expert in sexual medicine a new opportunity to treat the severe suffering of many patients.

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Footnote

Conflicts of Interest: Dr. Mcmahon is a consultant, investigator and speaker for Johnson & Johnson, Janssen Cilag, Menarini, Ixchelsis, Absorption Pharmaceuticals, Neurohealing and Plethora.

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