45 Sexual Function in Men and Women with Diabetes

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Keypoints

- The prevalence of erectile dysfunction (ED) in men with diabetes increases with age and is about 35–50% overall.
- Penile erection occurs as a result of engorgement of the erectile tissue following vascular smooth muscle relaxation in the corpus cavernosum mediated by nitric oxide (NO), which is derived from both parasympathetic nerve terminals and the vascular endothelium.
- ED in diabetes is largely brought about by failure of NO-mediated smooth muscle relaxation secondary to endothelial dysfunction and autonomic neuropathy.
- ED is an early indicator of endothelial dysfunction and a marker of increased cardiovascular risk.
- Phosphodiesterase 5 inhibitors are first-line treatment and act by inhibiting the breakdown of cyclic guanosine monophosphate, the second messenger in the NO pathway, and hence enhance erections under conditions of sexual stimulation.
- Other options are intracavernosal injection of prostaglandin E (alprostadil), transurethral alprostadil, vacuum therapy and surgical insertion of penile prostheses.
- In women with diabetes, sexual dysfunction is less common and usually undeclared, but there is an increased risk of vaginal dryness and arousal disorder.
- Contraception and family planning are especially important in women with diabetes. Although there is little consensus amongst diabetes professionals about the preferred method of contraception for women with diabetes, it appears that most currently available methods of contraception are suitable.
- Hormone replacement therapy (HRT) can be considered for treating menopausal symptoms in women with diabetes on a short-term basis, but HRT is not justified in asymptomatic women.

Male erectile dysfunction

The advent of effective oral treatments has changed the management of erectile dysfunction (ED) in diabetes considerably. Diabetologists and general practitioners can now offer treatments that are easy to use and generally effective. This change, however, has been a long time coming. As recently as 1993, ED was regarded as the most neglected complication of diabetes [1]. Since then, there has been a transformation in attitudes to the subject, in which diabetes professionals have led the way. Previously, ED was generally believed to be psychogenic in origin, even when associated with diabetes, and hence the management was considered to be the preserve of psychosexual counselors. We now accept that ED is a complications of diabetes that can and should be managed by diabetes professionals.

Physiology of erectile function

Tumescence is a vascular process under the control of the autonomic nervous system. The erectile tissue of the corpus cavernosum behaves as a sponge, and erection occurs when it becomes engorged with blood. As shown in Figure 45.1, dilatation of the arterioles and vasculature of the corpus cavernosum leads to compression of the outflow venules against the rigid tunica albuginea [2,3]. Thus, smooth muscle relaxation is the key phenomenon in this process, as it leads to increased arterial inflow and reduced venous outflow [4]. The process is under the control of parasympathetic fibres, which were previously known as non-adrenergic non-cholinergic neurones, as the neurotransmitter was unknown; but it is now clear that nitric oxide (NO) is the agent largely responsible for smooth muscle relaxation in the corpus cavernosum. It is produced both in the parasympathetic nerve terminals and is generated by NO synthase in the vascular endothelium. Within the smooth muscle cell of the corpus cavernosum, NO stimulates guanylate cyclase, leading to increased production of the second messenger, cyclic guanosine monophosphate (cGMP), which induces smooth muscle relaxation, probably by opening up calcium channels (Figure 45.2) [5,6].

There is some evidence that neuronally derived NO is important in initiation, whereas NO from the endothelium is responsible for maintenance of the erection [7].

Pathophysiology of erectile dysfunction in diabetes

In men with diabetes there is evidence that ED is caused by failure of NO-induced smooth muscle relaxation caused by both autonomic neuropathy and endothelial dysfunction [7,8]. Many men with diabetes report that in the early stages they do not have a

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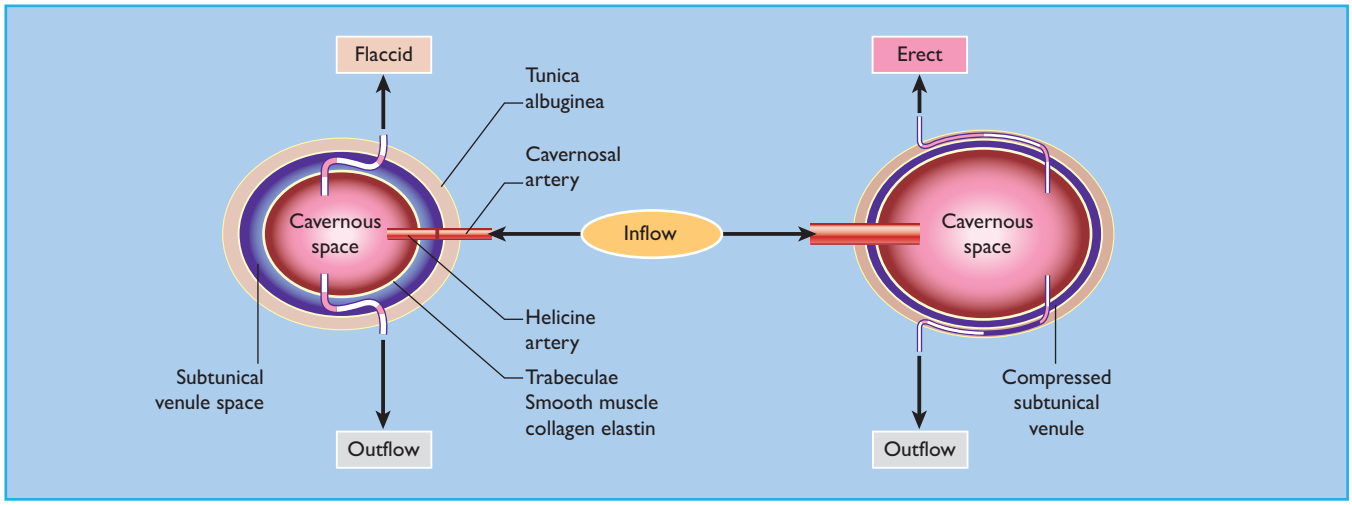

Figure 45.1 Diagrammatic representation of the corpus cavernosum. During tumescence, dilatation of the helicine and cavernosal arteries produces expansion of the cavernosal space and compression of the outflow venules against the rigid tunica albuginea.

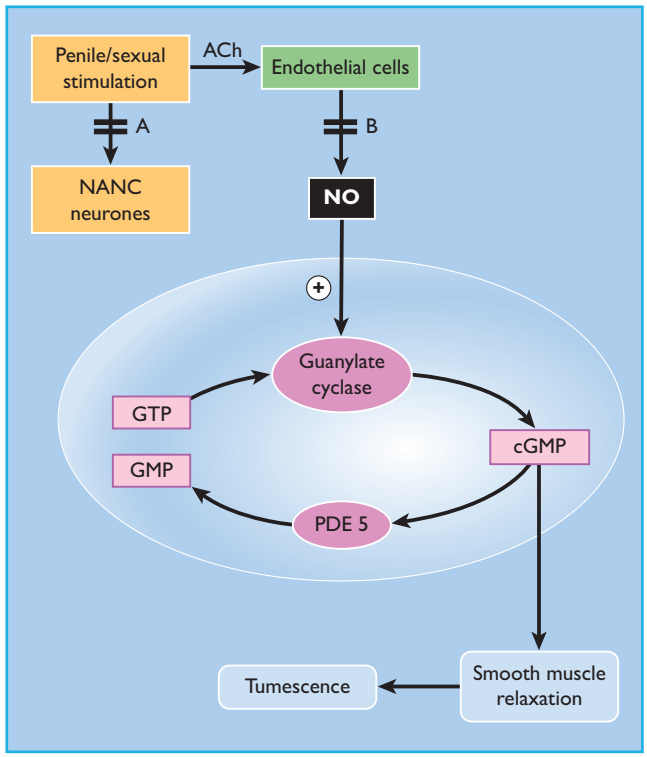

Figure 45.2 Pathophysiology of erectile function in diabetes. Diagrammatic representation of the pathways leading to the relaxation of a corpus cavernosal smooth muscle cell. In diabetes, there are defects in nitric oxide-mediated smooth-muscle relaxation from neuropathy of the non-adrenergic non-cholinergic (NANC) fibers (a) and endothelial dysfunction (b). ACh, acetylcholine; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; PDE 5, phosphodiesterase type 5.

problem initially achieving an erection but that they cannot maintain it. This would suggest that in these individuals failure of endothelium-derived NO occurs before significant autonomic neuropathy.

More recently, other potential abnormalities have been described which may contribute to the development of ED in diabetes. Endothelium-derived hyperpolarizing factor (EDHF) has a role in endothelium-dependent relaxation of human penile arteries [9] and this is significantly impaired in penile resistance arteries in men with diabetes [10]. Impaired EDHF responses might therefore contribute to the endothelial dysfunction of diabetic erectile tissue.

A further body of evidence suggests increased oxygen-free radical levels in diabetes may reduce the vasodilator effect of NO. In particular, the formation of products of non-enzymatic glycosylation to produce advanced glycosylation end-products (AGEs) generates reactive oxygen species which impairs NO bioactivity [11]. In animal models, inhibition of AGE formation improves endothelium-dependent relaxation and restores erectile function in diabetic rats [12,13].

Other pathophysiologic changes known to occur in diabetes have been postulated to contribute to ED. Non-enzymatic glycation of proteins has been reported to impair endothelium-dependent relaxation of aorta in rats [13,14].

Other factors, not limited to diabetes, may also contribute to the development of ED in men with diabetes. Structural changes associated with large vessel disease are commonly associated with ED in diabetes; however, this is usually associated with functional changes of widespread endothelial dysfunction in diabetes and it is difficult to separate the relative importance of the two factors.

Other factors contributing to erectile dysfunction in diabetes

In addition to endothelial dysfunction and autonomic neuropathy, ED is associated with other conditions common in diabetes, such as hypertension and large-vessel disease [15]. Furthermore, men with diabetes are more likely to be taking medications that can impair erectile function (Table 45.1). Antihypertensive agents

Table 45.1 Medications associated with erectile dysfunction.

Antihypertensives
Thiazide diuretics
Beta-blockers
Calcium-channel blockers
Angiotensin-converting enzyme (ACE) inhibitors
Central sympatholytics (methyldopa, clonidine)

Antidepressants
Tricyclics
Monoamine oxidase inhibitors
(NB: selective serotonin re-uptake inhibitors can cause ejaculatory problems)

Major tranquillizers
Phenothiazines
Haloperidol

Hormones
Luteinizing hormone-releasing hormone (goserelin, buserelin)
Estrogens (diethylstilbestrol/stilbestrol)
Anti-androgens (cyproterone)

Miscellaneous
5-alpha reductase inhibitors (finasteride)
Statins (simvastatin, atorvastatin, pravastatin)
Cimetidine
Digoxin
Metoclopramide
Allopurinol
Ketoconazole
Non-steroidal anti-inflammatory agents
Fibrates

Drugs of "abuse"/"social" drugs
Alcohol
Tobacco
Marijuana
Amfetamines
Anabolic steroids
Barbiturates
Opiates

Table 45.2 Conditions associated with erectile dysfunction.

Psychologic disorders
Anxiety about sexual performance
Psychologic trauma or abuse
Misconceptions
Sexual problems in the partner
Depression
Psychoses

Vascular disorders
Peripheral vascular disease
Hypertension
Venous leak
Pelvic trauma

Neurologic disorders
Stroke
Multiple sclerosis
Spinal and pelvic trauma
Peripheral neuropathies

Endocrine and metabolic disorders
Diabetes
Hypogonadism
Hyperprolactinemia
Hypopituitarism
Thyroid dysfunction
Hyperlipidemia
Renal disease
Liver disease

Miscellaneous
Surgery and trauma
Smoking
Drug and alcohol abuse
Structural abnormalities of the penis

are commonly reported to be associated with ED, although much of the evidence is anecdotal; beta-blockers and thiazide diuretics are the most commonly reported culprits [16], alpha-blockers perhaps have the lesser risk [17]. Finally, it should be remembered that there are many other potential causes of ED unrelated to diabetes, from which men with diabetes are not immune (Table 45.2).

Clinical aspects of erectile dysfunction in diabetes

ED becomes more common with age. In a population-based study in Massachusetts, USA, the prevalence of complete erectile failure was reported to be 5% in men in their forties and 15% in those over 70 years [15]. The prevalence in diabetic men is significantly higher and also increases with age. In a survey of men attending a hospital diabetic clinic in the UK, the prevalence of

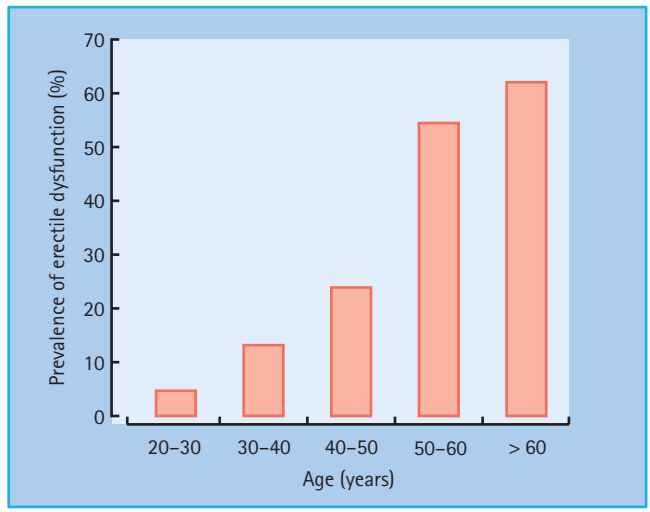

Figure 45.3 The prevalence of erectile dysfunction by age of men attending a hospital diabetic clinic [1].

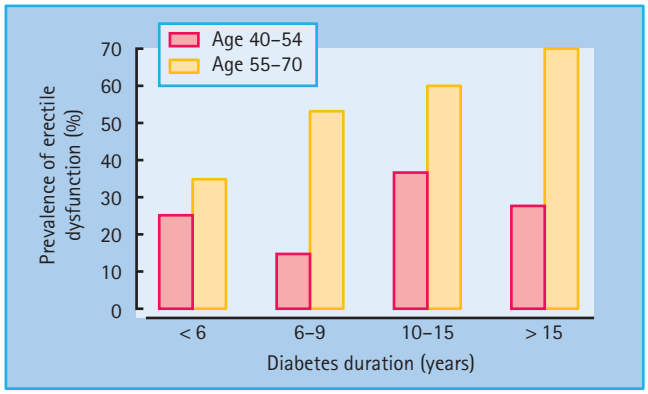

Figure 45.4 The prevalence of erectile dysfunction by duration of diabetes in a population-based study [19].

ED increased from 13% amongst 30-year-olds to 61% amongst men aged over 60 years (Figure 45.3) [1]; overall, the prevalence was 38%. The prevalence of ED in diabetes in a general practice population was reported to be even higher, at 55% [18]. These data would suggest that ED is the most common clinically apparent complication of diabetes in men.

The presence of other medical conditions increases the risk of ED. A population-based survey of 600 men in Brazil, Italy, Japan and Malaysia in 2000 examined the prevalence of ED and its relationship to other diseases and lifestyles. The prevalence of ED among men with diabetes rose from 25% at age 40–44 years to 70% at age 65–70 years [19]. Cardiovascular disease increased the risk of ED. The prevalence was 31.7% in men with diabetes only, 40% in men with diabetes and heart disease and 46.5% in those with diabetes and hypertension. The prevalence also increased with duration of diabetes (Figure 45.4). Men with diabetes who smoked and reported below average levels of physical activity had a fourfold increase in the prevalence of ED.

Erectile dysfunction as a risk factor for cardiovascular disease

There is convincing evidence of an association of between ED and cardiovascular disease [20–22]. This may be because they share common risk factors. Increased waist measurement and reduced physical activity, both important risk factors for ischemic heart disease, considerably increase the risk of ED [23–25]. The risk of ED is also increased in men with hyperlipidemia [26].

Recent studies have suggested that the association between ED and cardiovascular disease may be brought about by more than shared risk factors and may arise because they are both manifestations of endothelial dysfunction. There has been considerable interest in recent years in the role of the vascular endothelium in the pathogenesis and progression of atherosclerosis [27]. It is clear that the endothelium has important and complex endocrine and paracrine functions, and one of its most important products is NO (previously known as endothelium-derived relaxing factor). NO possesses potent antiatherogenic properties, inhibits platelet aggregation and regulates vascular tone [28]. As described above, NO derived from both nerve terminals and the vascular endothelium has a central role in the physiology of erection. Therefore, there are theoretical grounds to believe that the ED might be an early marker of endothelial dysfunction and hence an important risk factor for cardiovascular disease. There is now good evidence that ED is an early marker of endothelial dysfunction [29]. Thus, the association between ED and increased cardiovascular risk may be a case of shared common soil, in particular endothelial dysfunction and microvascular disease. In practical terms this means cardiovascular risk should be assessed in any man with ED whether diabetic or not. A man with type 2 diabetes (T2DM) and ED has approximately double the risk of developing coronary heart disease than a similar man without ED [22].

Smoking and alcohol consumption

Smoking greatly increases the risk of developing ED. A follow-up of the Massachusetts Male Aging Study reported that cigarette smoking almost doubled the risk of developing ED after about 7 years [15]. A similar finding was reported by the large Health Professionals' Follow-up Study [24].

In contrast to tobacco, it is well established that moderate alcohol consumption reduces the risk of a cardiovascular event. It is interesting that drinking alcohol in moderation also appears to reduce the risk of becoming impotent [23].

Quality of life issues

That ED can significantly worsen a man's quality of life is not in doubt. Unfortunately, there are few good data to show objectively the impact ED can have on quality of life measures, and even fewer to show the impact of treating ED. A survey by the Impotence Association found symptoms of lowered self-esteem and depression in 62% of men; 40% expressed concern with either new or established relationships, and 21% blamed it for the break-up of a relationship [30]. In another series in general practice, it was reported that 45% of men with diabetes stated that they thought about their ED all or most of the time, 23% felt that it severely affected their quality of life and 10% felt it severely affected their relationship with their partner [18].

Assessment and investigation of erectile dysfunction in diabetes

Clinical assessment

In most cases, an impotent man will have taken a long time to pluck up the courage to discuss his problem with a doctor and will undoubtedly be anxious. Almost invariably, however, once the subject has been broached, men with ED and their partners do not usually have any difficulty discussing the problem. A description of the nature of the ED should be obtained, not least to ensure that the patient is complaining of ED and not another related problem, such as premature ejaculation. The key features in the history of ED are listed in Table 45.3. Ideally, the man's partner should be present, but most men attend the consultation alone. If the partner is present, talking to her without the patient present can reveal interesting and useful insights into the problem.

Table 45.3 Key features in the clinical history of erectile dysfunction in diabetes.

Onset usually gradual and progressive
Earliest feature often inability to sustain erection long enough for satisfactory intercourse
Erectile failure may be intermittent initially
Sudden onset often thought to indicate a psychogenic cause (but little evidence to support this)
Preservation of spontaneous and early morning erections does not necessarily indicate a psychogenic cause
Loss of libido consistent with hypogonadism, but not a reliable symptom. Impotent men often understate their sex drive for a variety of reasons

Table 45.4 Key physical signs to note on examination of the patient with erectile dysfunction.

Any features of hypogonadism
Manual dexterity – may preclude physical treatment (e.g. intracavernosal injection)
Protuberant abdomen
External genitalia:
Presence of phimosis
Testicular volume

General physical examination may give clues as to the etiology of ED and the choice of treatment. The key features of the physical examination are listed in Table 45.4.

Investigation of erectile dysfunction in diabetes

The suggested investigations of ED in diabetes are listed in Table 45.5. It is now widely accepted that it is not helpful to try to determine whether or not ED is psychogenic in origin, particularly when managing a man with diabetes and ED. Few investigations are needed, but it is worth excluding other treatable causes of ED: in practical terms, hypogonadism is the only treatable one. There is probably no significant relationship between diabetes and hypogonadism, and therefore gonadal function should only be assessed in men with diabetes and ED if it is considered worthwhile looking for a coincidental problem causing hypogonadism. Some men presenting with ED will not have attended any form of clinic for many years, so the consultation provides an opportunity to address other health issues. For the reasons given above, consideration should be given to assessing the patient's cardiovascular status. The consultation also provides an opportunity to address the management of the patient's diabetes.

General advice

Most men with diabetes and their partners seeking treatment for impotence are middle-aged, have been married for many years and require only simple common-sense advice. Specialist psychosexual counseling is not needed for most couples: several series

Table 45.5 Investigation of erectile dysfunction in diabetes.

Serum testosterone if libido reduced or hypogonadism suspected (ideally taken at 9 am)
Serum prolactin and luteinizing hormone if serum testosterone subnormal
Assessment of cardiovascular status if clinically indicated:
Electrocardiography (ECG)
Serum lipids
Glycosylated hemoglobin, serum electrolytes if clinically indicated

have reported that diabetologists can offer an effective service for the treatment of ED without the support of psychosexual counselors [31–34]. It is important that the cause of the ED is explained, as many patients will blame themselves. They should be advised that if they wish to resume sexual relations they will require long-term treatment, as spontaneous return of erectile function in diabetes occurs only rarely [35].

Treating ED in an attempt to save a failing relationship is rarely successful and may make the situation worse. The assistance of a suitably qualified psychosexual counselor should be considered in this situation. Referral to a counselor should also be considered if there is any suggestion of severe anxiety, loss of attraction between partners, fear of intimacy or marked performance anxiety. Any other medical problems should be addressed. Improving poor metabolic control may help general well-being, but poor control should not be used as a reason to refuse or delay treatment. Patients who smoke should be advised to stop for reasons of general health, although there is no good evidence that stopping smoking will improve erectile function in a man with diabetes and ED.

Many men with diabetes will be taking medication known to cause ED. Experience has shown that changing the treatment in an attempt to improve sexual function rarely works and may cause delays and frustration for the patient. It is therefore not advisable unless there is a strong temporal relationship between starting treatment and the onset of ED.

Treatment options

The advent of effective oral therapies has transformed the management of ED. These should be offered as first-line therapy to men with diabetes and ED, and the other treatment options should be reserved for those in whom oral therapy is contraindicated or ineffective.

Oral agents

Phosphodiesterase 5 inhibitors

Phosphodiesterase type 5 (PDE 5) is an enzyme found in smooth muscle, platelets and the corpus cavernosum. The mechanism of action of PDE 5 inhibitors is shown in Figure 45.2. During tumescence, there is an increase in the intracellular concentrations of NO, which produces smooth muscle relaxation via the second messenger cGMP. This is broken down in turn by PDE 5. Hence, PDE 5 inhibitors can enhance erections under conditions of

sexual stimulation. There are currently three PDE 5 inhibitors licensed for the treatment of ED: sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra).

Clinical trial data. Sildenafil was the first PDE 5 inhibitor. Early small trials showed it was a highly effective treatment for ED in men with and without diabetes [36,37]. The first large study was published in 1998. A total of 532 men with ED of mixed etiology were studied. In the group given sildenafil, 69% of all attempts at intercourse were successful, compared with 22% in those given placebo [38]. Other studies in men with ED of mixed etiology have shown success rates of 65–77% [39,40]. Studies of sildenafil in other patient groups have reported success rates of approximately 70% in hypertension [41], 76% in spinal cord injury [42], 63% in spina bifida [43] and 40% following radical prostatectomy [44].

In men with diabetes, the success rates for sildenafil have been reported to be 56–59% in the treatment of ED [37,45]. A study in elderly men reported success rates of 69% overall and 50% in subjects with diabetes [46]. Most of these studies of sildenafil have been short-term. A trial examining the long-term efficacy of sildenafil in men with ED from a variety of causes reported that only 52% continued to use it after 2 years [47]. This figure may seem surprisingly low, but it is certainly considerably higher than for any other type of ED treatment.

Other PDE 5 inhibitors

Sildenafil was soon followed by tadalafil (Cialis) [48–50] and vardenafil (Levitra) [51,52]. All three appear to be similar in efficacy and safety but there are differences in duration of action and adverse effect profiles as described below.

Adverse effects. The most common adverse effects related to PDE 5 inhibitors are headache, dyspepsia and flushing. Headache and flushing might be expected, as they are vasodilators. The dyspepsia is usually mild and may be caused by relaxation of the cardiac sphincter of the stomach.

Abnormal vision is experienced by about 6% of men taking sildenafil; this may be because the drug has some activity against PDE 6, which is a retinal enzyme. Of more concern are the reports of non-arteritic anterior ischemic optic neuropathy (NAION). This is a rare syndrome characterized by sudden, sometimes unilateral, often reversible, visual loss. Since 2002 there have been case reports of this condition occurring in association with the use of PDE 5 inhibitors, particularly sildenafil [53,54]. NAION is rare but potentially serious as it can, exceptionally, lead to blindness. It would appear it is more common in men with increased cardiovascular risk [55]. The manufacturers of sildenafil estimated the incidence of NAION in 13 000 men receiving sildenafil from pooled safety data from clinical trials and observational studies to be 2.8 cases per 100 000 patient-years of sildenafil exposure [56]. The authors reported this to be similar to estimates reported in general US population samples (2.52 and 11.8 cases per 100 000 men aged over 50 years). It is therefore unknown if PDE 5 inhibitor use increases the risk of NAION but in any case it is a very rare condition and should not discourage the appropriate use of these agents.

Table 45.6 Adverse effects of phosphodiesterase 5 (PDE 5) inhibitors (%). The prevalence quoted for each adverse effect is for the top dose used in each study.

	Sildenafil [59,60]	Tadalafil [59,61,62]	Vardenafil [63,64]
Headache	8.1–9.3	8.0–21	5–11
Flushing	7.4–8.1	3.0–9.0	5.4–10
Back pain	2.5	4.6–9.0	0
Dyspepsia	2.7–3.0	4.1–17	2.3
Nasal congestion	2.7–4.1	2.0–5	10
Dizziness	2.5	1.6	
Diarrhea	2.5	0.8	
Abnormal vision	1.4	0	
Muscle cramps	4.1	3–7	

The adverse events from the key trials of PDE 5 inhibitors in men with diabetes are given in Table 45.6. In all the studies, the discontinuation rate from adverse effects has been very low.

Reasons for PDE 5 inhibitor non-responsiveness. The mechanism of action of sildenafil would suggest that it would be ineffective without the presence of sufficient bioavailable NO in the penile vasculature. Thus, either significant autonomic neuropathy or endothelial dysfunction would be expected to reduce the efficacy of a PDE 5 inhibitor. Slightly surprisingly, two small studies have reported no differences in the presence of autonomic or endothelial function between sildenafil "responders" and "non-responders" [29,57]. It has been reported that failure to respond to sildenafil is more likely in men with long-standing and severe ED [58]; however, no single factor precludes a successful outcome, and in practical terms it is worth trying sildenafil in all men with ED unless there is a contraindication.

Cardiovascular safety of PDE 5 inhibitors. The launch of sildenafil, the first PDE 5 inhibitor, was soon followed by case reports of cardiovascular events and deaths associated with its use. By contrast, there is now good evidence that PDE 5 inhibitors are not associated with increased cardiovascular risk [65,66]. A questionnaire survey of over 5000 sildenafil users reported that adverse cardiovascular events were no more frequent than expected for a comparable population [67]. A retrospective analysis of 36 clinical trials of tadalafil involving over 14 000 men reported no increase in cardiovascular adverse events [68]. Indeed, there is accumulating evidence that PDE 5 inhibitors reduce blood pressure slightly and improve endothelial function [66,69].

Restoring sexual function, however, is not completely without risk. Sexual activity, like any form of physical activity, can precipitate cardiovascular events in those at risk. A large case–control

study reported the risk of a cardiovascular event in the 2 hours after intercourse was increased by 2.5 fold in healthy subjects and by 3 fold if there was a history of previous myocardial infarction [70]. Although the absolute risk remains very small, the issue of cardiovascular safety must be addressed in all men before treating ED. Jackson *et al.* [65] have suggested a classification scheme for assessing cardiovascular risk in men undergoing treatment for ED, those with the highest risk should be referred for specialist cardiac evaluation while the lowest risk group could be managed in primary care.

Drug interactions with PDE 5 inhibitors. PDE 5 inhibitors can be used safely in patients taking a wide range of other drugs but there are several potential important interactions. They are contraindicated in the presence of any nitrate therapy (including nicorandil) as the combination can cause profound hypotension. A patient taking nitrates seeking treatment for ED can be offered alternatives to PDE 5 inhibitors or the nitrates can be stopped or changed to an alternative therapy. Nitrates are a symptomatic treatment with no prognostic implications and so this is possible in most cases but should be done in consultation with a cardiologist in all but the most straightforward cases.

Nitrate therapy should not be given within 24 hours of taking sildenafil or vardenafil and at least 48 hours of taking tadalafil. If angina develops during or after sexual activity following the use of a PDE 5 inhibitor, the patient should be advised to discontinue any sexual activity and stand up as this reduces the work of the heart by reducing venous return.

PDE 5 inhibitors should be used with caution in patients who take alpha-blockers because the combination may lead to symptomatic hypotension in some patients. Patients should be stable on alpha-blocker therapy before initiating sildenafil which should be initiated at the lowest dose [66].

Comparison of PDE 5 inhibitors. The three currently available PDE 5 inhibitors, sildenafil, vardenafil and tadalafil, are all similar in efficacy and safety. Their side effect profiles differ slightly but the most notable difference is the longer half-life of tadalafil. Thus, a single dose of tadalafil offers the potential to restore erectile function to normal for 2 days and thereby remove the need for medication to be taken each time prior to sexual activity. The choice between this form of treatment and on-demand dosing is largely a matter of patient choice. Patient preference studies of agents with differing dosing instructions are difficult to perform in a blinded fashion. Several have been reported and have generally shown a preference for tadalafil over sildenafil [59,71–74].

How to use PDE 5 inhibitors. These agents should be taken orally about 1 hour before sexual activity. This period can be shortened if taken on an empty stomach. After the 1-hour period, there is a "window of opportunity" when sexual activity can take place. For sildenafil and vardenafil this is at least 4 hours but may be over 8 hours [75]. For tadalafil the window of opportunity may last 48 hours. Men with diabetes usually require the maximum recommended dose. Patients should be warned that the drug only works in conjunction with sexual stimulation.

Management of PDE 5 inhibitor non-responsiveness. A large proportion of men with diabetes and ED will not respond to PDE 5 inhibitors and there are many potential reasons for this. PDE 5 inhibitors require a degree of NO tone to be effective, therefore severe endothelial dysfunction of autonomic neuropathy might be expected to reduce their efficacy; however, one study reported that neither autonomic neuropathy nor endothelial dysfunction predicted sildenafil responsiveness. The only significant factor that predicted the response to treatment was the initial degree of ED [29]. In practical terms, no single factor should preclude a trial of PDE 5 inhibitor therapy in a man without a contraindication.

Much has been written on the best approach for dealing with men who do not respond to a PDE 5 inhibitor but, unfortunately, mostly based on limited evidence. It has been suggested that if appropriate advice is given and sufficient attempts at intercourse made, many men previously labeled as non-responders can be treated successfully with PDE 5 inhibitors. One study reported that intercourse success rates reached a plateau after eight attempts so men with ED should try at least eight times with a PDE5 inhibitor at the maximum recommended dose before being considered a non-responder [76].

Hypogonadism should always be considered in dealing with men with ED who do not respond. Hypogonadism caused by confirmed pituitary or testicular disease usually responds well to treatment. The management of the borderline hypogonadism of the aging male is more controversial but there is some evidence that testosterone replacement in this situation can improve ED as a sole treatment [77] and enhance the response to PDE 5 inhibitors [78–80].

Other oral therapies

Apomorphine

Apomorphine has been in use for many years. It is a centrally acting D1/D2 dopamine agonist that acts on the paraventricular nucleus of the thalamus early in the cascade that leads to erection. Among its several properties, it is a potent inducer of nausea, and this has previously limited its use as a therapeutic agent. A sublingual formulation is licensed in Europe as a treatment of ED. This preparation has no first-pass metabolism, and it rapidly produces therapeutic blood levels. Studies of the sublingual preparation have suggested that it is effective in inducing erections in about 50% of attempts and has acceptable levels of adverse effects [81]. To date, there have been no published trials of apomorphine in men with diabetes and it is not widely used in diabetic practice.

Various oral agents have been tried as treatments for ED in the past, including trazodone, yohimbine and phentolamine. The data on all of them are limited and none has stood the test of time. Testosterone should only be used to treat ED secondary to confirmed hypogonadism.

Figure 45.5 Alprostadil self-injection pen device.

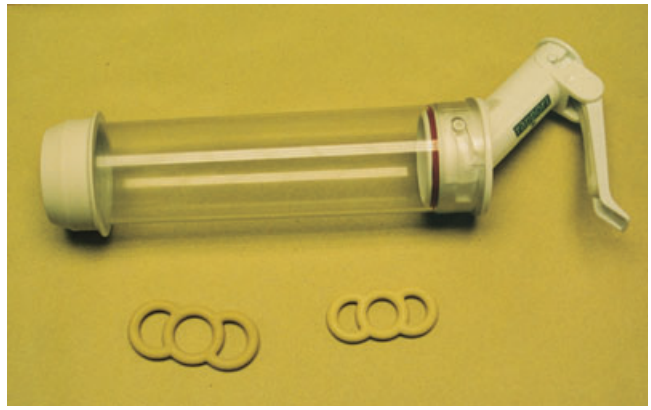

Figure 45.6 A typical vacuum device with constriction rings.

Table 45.7 Instructions to medical staff for treating prolonged erections caused by prostaglandin E1.

- Do not delay treatment beyond 6 hours
- Using aseptic technique, aspirate 20–25 mL blood from the corpus cavernosum (19 or 21 gauge butterfly needle)
- Repeat the above on the opposite side of the penis if detumescence does not occur
- If still unsuccessful, inject 0.5–1.0 mL of a 300-µg/mL solution of phenylephrine every 5–10 minutes (maximum dosage 5 mL) into the corpus cavernosum. If necessary, this may be followed by further aspiration of blood through the same needle. Extreme caution is necessary in those patients taking monoamine oxidase inhibitors, as a hypertensive crisis may result. Use carefully in those with coronary heart disease, uncontrolled hypertension or cerebral ischemia. Monitor pulse rate and blood pressure throughout
- If the above are unsuccessful, refer for urgent surgical treatment, such as a shunt procedure

Intracavernosal injection therapy

The technique of intracavernosal self-injection was first described in 1982 by Brindley [82], using phentolamine, although the French urologist, Virag [83], who used papaverine, was first to publish. Papaverine was more effective than phentolamine, but was an unlicensed treatment; it was superseded by alprostadil (prostaglandin E), which was licensed for the treatment of ED in 1996.

Alprostadil is supplied in a self-injection pen device, which is easy to use, and supplied with excellent instructions (Figure 45.5). In spite of this, most studies show that self-injection therapy has a disappointingly high long-term discontinuation rate [84–86]. Self-injection treatment carries a small risk of priapism (a sustained unwanted erection). Although an infrequent complication, priapism is an important one, as it must be treated within 6 hours by aspirating blood from the corpus cavernosum. Patients undertaking self-injection must be warned of this potential problem and given instructions on what to do should it occur (Table 45.7).

Local adverse reactions, such as penile pain, are relatively common with self-injection therapy. Prolonged papaverine use may lead to fibrosis in the penis, but this has only rarely been reported with alprostadil [87].

More recently the combination of vasoactive intestinal polypeptide and phentolamine has been licensed for use under the name of Invicorp. It appears to be a potentially useful treatment for ED [88,89].

Transurethral alprostadil (MUSE)

Many men find injection therapy unacceptable because it requires injecting the penis. Transurethral administration of the vasoactive agent would appear largely to overcome this problem. The principle is simple. A slender applicator is inserted into the urethra to deposit a pellet containing alprostadil in polyethylene glycol. This gradually dissolves, allowing the prostaglandin to diffuse into the corpus cavernosum. In a placebo-controlled study of 1511 men with ED of mixed etiology, it was reported that 65% were able to have intercourse using this system [90]. The results in the 240 men with diabetes in the study were similar [91]. The most common side effect was penile pain, which occurred in 10.8% of applications. Hypotension was reported by 3.3% of the men receiving alprostadil. Priapism and penile fibrosis were not reported. A more recent study reported that most men found transurethral alprostadil less acceptable and efficacious than intracavernosal injection [92], and the long-term usage has been disappointing [93].

Vacuum therapy

Vacuum devices became widely available in the 1970s. They consist of a translucent tube, which is placed over the penis, and an attached vacuum pump (Figure 45.6). The air is pumped out of the tube, and the negative pressure draws blood into the erectile tissue, producing tumescence. A constriction band (which has previously been placed over the base of the tube) is then slipped off to remain firmly around the base of the penis so as to maintain the erection, and the tube is then removed. The devices require a little practice and some dexterity, but most couples are able to

use them satisfactorily. Trials of vacuum therapy have reported success rates of approximately 70% in men with and without diabetes, suggesting it is an effective treatment, provided couples are prepared to use them [94–97].

Vacuum devices are safe and effective treatments, and inexpensive to use after an initial outlay (in the UK) of about £100–250. The side effects are discomfort from the constriction band, failure to ejaculate and a cold penis (reported by the female partner). Many couples find the use of vacuum devices unacceptable, and since the introduction of newer treatments their use has declined; however, they still have a role in men who do not respond or who cannot use other treatments.

Surgery

In spite of recent advances in the management of ED, some men will not be able to use the available treatment options. There will therefore always be a limited role for surgery.

The surgical options available are:

1 The insertion of penile prostheses;
2 Corrective surgery for associated Peyronie disease or post-injection corporal fibrosis;
3 Venous and arterial surgery.

Discussion of vascular and corrective surgery of the penis is best left to a specialist urology textbook, but a general practitioner or diabetes physician needs to know which patients might benefit by referral for insertion of a penile prosthesis. This form of surgery is best reserved for men in whom conventional treatments have failed and who are keen to resume full sexual activity.

Counseling of the patient, and whenever possible his partner, is extremely important, particularly about the choice of prosthesis. The patient's or couple's wishes are very important factors in device selection, as is the cost of the prosthesis. In the UK, many hospital trusts will only pay for the malleable prostheses and not for the insertion of the considerably more expensive inflatable ones.

Patients must be warned regarding postoperative pain or discomfort and the potential for reoperation. Patients will need to restrict physical activity and refrain from intercourse for between 4 and 6 weeks after the operation. They should be warned about the possible complications of infection, erosion and prosthesis failure, and that these problems usually require device removal. It is also very important that the patient and his partner are aware that the erection produced by a prosthesis is different from a normal erection, depending very much on the type of prosthesis chosen. It is useful to show patients examples of the prostheses (Figure 45.7) and to describe how they are inserted and the mechanism of action.

There is uncertainty as to whether men with diabetes are at higher risk of infection than men without diabetes after insertion of a penile prosthesis, but there is a consensus that, should infection occur, it is more serious [98]. Good preoperative control of diabetes is important to minimize the risk. Most published series of well-selected groups of men who have undergone penile prosthesis insertion have reported acceptable results, with good levels of patient satisfaction [99].

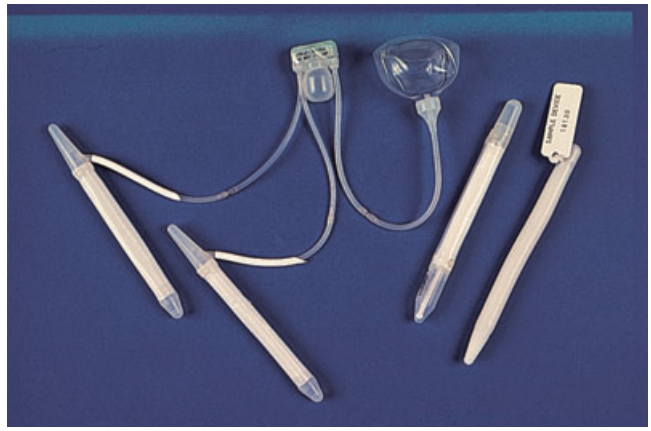

Figure 45.7 Examples of penile prostheses.

Organization of the management of ED

Traditionally, ED has been managed in a dedicated ED clinic, often run by a urologist. The advent of effective oral therapies has made the management much simpler, so that ED in diabetes can usually be managed by any physician or general practitioner. A physician considering treating ED will have to decide whether to run a separate ED clinic or to see the patients in a routine diabetic clinic. Such a decision will depend on local resources and circumstances but it is certainly possible to manage ED in a diabetic clinic. If this is to be done, it is advisable to have patient information literature on ED available. There are several excellent pamphlets produced by pharmaceutical companies and national diabetes organizations such as Diabetes UK. It is often wise to let the patient take away the literature to read and to consider the matter, with treatment being started at a subsequent visit.

Managing ED in primary care

There are considerable advantages for the treatment of ED in general practice. A general practitioner is more likely to know and understand a patient's particular circumstances. Men with ED may be less intimidated in seeking help from their family practitioner than from a hospital specialist or sexual therapist. Little specialized equipment is required, so there is no reason why interested general practitioners should not effectively treat the majority of men presenting with ED.

As with many disorders encountered in primary care, the general practitioner may choose to manage the problem in a standard consultation with the patient. Others may choose to refer their patients to a fellow partner or colleague with a particular interest in ED or to their practice nurse, who may have received appropriate training in the assessment of patients with ED.

When a man presents with ED, his general practitioner has an opportunity to consider other health issues and screen for under-

lying causes. ED is often associated with conditions that benefit from early detection such as diabetes, hypertension and hyperlipidemia. It is therefore important to consider general health issues and to address lifestyle factors.

The specialist erectile dysfunction service

Although most men with ED will be managed in primary care, there is still a role for a specialist ED service. It is likely that these clinics will mainly treat men who have failed to respond to oral therapies and that they will maintain expertise in the use of other treatments, such as intracavernosal injection therapy and vacuum devices, referring patients when necessary to urologic surgeons for penile prosthesis insertion.

Conclusions on male sexual dysfunction

NO-mediated relaxation of the smooth muscle of the corpus cavernosum is the key phenomenon leading to penile erection. In diabetes, there is impairment of NO production by autonomic nerve terminals (caused by autonomic neuropathy) and by endothelial cells (caused by endothelial cell dysfunction). Sildenafil and other PDE inhibitors work by inhibiting the breakdown of cGMP, the second messenger in the NO pathway, and hence enhance erections under conditions of sexual stimulation. These agents are safe and effective treatments and can be used to treat ED in a diabetic clinic or in general practice.

Female sexual dysfunction

Male sexual dysfunction has been described as the most neglected complication of diabetes. However, there has been considerably more interest in, and research into, the sexual dysfunction of men as compared to women. There may be good reasons for this. In physiologic terms, the female equivalent of male ED is reduced vasocongestion of the vulva and vagina, leading to impaired arousal and reduced vaginal lubrication. Failure to achieve an erection makes sexual intercourse impossible, but reduced vaginal lubrication is easily overcome with simple treatments such as lubricating creams and may not even be considered to be abnormal by a postmenopausal woman.

In a review published in 1998, Enzlin *et al.* [100] undertook an analysis of 15 studies carried out in the area of female sexuality in diabetes since 1971. They reported that the prevalence of impaired sexual arousal and inadequate lubrication was between 14% and 45% in women with diabetes, which was significantly higher than in controls without diabetes [100]. In contrast, there was little evidence of an increased risk of dyspareunia or problems with orgasm in women with diabetes. Thus, it would appear that women with diabetes admit to specific sexual dysfunctions when they are asked, but it is the universal experience of diabetologists that women with diabetes rarely complain of sexual problems. That a problem is not often volunteered by patients does not mean it is not significant or worthy of research.

More recent studies in women with type 1 diabetes (T1DM) have shown similar findings. Enzlin *et al.* [101] reported that 27% of diabetic women had sexual dysfunction compared to 14% in controls but only reduced lubrication was significantly different between the groups. The same group found that in women with T1DM sexual dysfunction was more closely related to psychologic rather than somatic factors [102].

If vaginal lubrication is the female equivalent of tumescence, then vaginal dryness and impaired arousal may be related to failure of NO-mediated smooth muscle relaxation secondary to endothelial dysfunction and autonomic neuropathy. There has been very little research into the pathophysiology of sexual dysfunction in women, but several studies have reported, a little surprisingly, that there does not appear to be a strong relationship between neuropathy and female sexual dysfunction [103–106]. Anecdotally, women with severe autonomic neuropathy can have an excellent sex life, unlike men, so it is likely there are differences between men and women in the way the autonomic nervous system controls genital responses [107]. Little work has been carried out on the effect of other medical conditions or treatments on sexual function in women.

Drug therapy and female sexual dysfunction

The mechanism of action of PDE 5 inhibitors would suggest they might improve arousal and vaginal lubrication; however, trials of sildenafil for this purpose in non-diabetic women have shown conflicting results. In a small cross-over study of 53 premenopausal women, it was reported that sildenafil significantly improved the frequency of intercourse and enjoyment compared with placebo [108]. In contrast, a much larger study of 583 women with female sexual arousal disorder reported no difference between the sildenafil or placebo-treated groups [109]. One of the few studies published to date on the effect of sildenafil on sexual dysfunction in women with diabetes reported that the treated group had improved arousal and sexual enjoyment as well as clitoral blood flow compared with controls [110].

Many women attending a diabetic clinic will be over 50 years of age and some will have problems associated with the menopause, including vaginal dryness and dyspareunia. It can be difficult to distinguish the effects of the menopause from those of diabetes, but in practical terms the treatment is the same. Topical estrogen or simple lubricant gels are usually effective. Managing loss of libido in women with diabetes is more complex and beyond the scope of this chapter. It is much more likely to be caused by psychosocial and relationship issues rather than somatic problems.

Genitourinary infections in women with diabetes

Vaginal candidiasis is a common finding in women with diabetes, particularly if the blood glucose control is poor and probably because yeasts thrive in a glucose-rich environment. Severe infection can be very irritating and painful and can interfere with sexual intercourse. Infections usually respond to conventional antifungal creams and pessaries; resistant cases usually respond

to a single oral dose of fluconazole. To reduce the chances of reinfection, attempts should be made to improve diabetic control. The male partner may also need treatment for candidiasis for the same reason.

Other genital infections also occur in women with diabetes, but probably no more frequently than in the general population. These cases should be referred to the appropriate genitourinary service.

Conclusions on female sexual dysfunction

There are differences in the ways in which men and women respond to sexual dysfunction. Traditionally, the view has been expressed that men focus on physiologic function, while the quality of the relationship is more important to women. Such generalizations are now considered a little dangerous, but there is no doubt that in women, psychologic factors are more important than the minor degrees of sexual dysfunction that occur in diabetes. When asked, women with diabetes admit to an increased prevalence of vaginal dryness and impaired arousal, but these are not common problems in the day-to-day management of diabetes. The treatment for these problems is the same for women either with or without diabetes. Other associated problems, such as vaginal candidiasis or estrogen deficiency, should be addressed. If there are relationship problems, referral to a counselor should be considered. The role of PDE 5 inhibitors remains uncertain in female sexual dysfunction, and further research is needed in this area.

Contraception

Contraception and family planning are especially important in women with diabetes. Poor glycemic control during the first trimester of pregnancy is associated with an increased risk of fetal morbidity and mortality [111–113]. It is therefore essential that women with diabetes are advised to plan their pregnancies and achieve strict control of their diabetes prior to conception (see Chapter 53).

Method of contraception

There is little consensus amongst diabetes professionals about the preferred method of contraception for women with diabetes. Neither the American Diabetes Association nor Diabetes UK has published recent guidance on the subject. Surveys of doctors in the UK [114] and Germany [115] have reported considerable variation among physicians for their recommended method of contraception for diabetic women. Most currently available methods of contraception are suitable for women with diabetes; however, certain factors should be taken into consideration before choosing any particular method.

Contraindications to pregnancy

As medical and obstetric care has improved, the list of contraindications to pregnancy in women with diabetes has shrunk (see Chapter 53). If pregnancy is contraindicated, sterilization should be considered.

The oral contraceptive pill

In a survey of 938 women with T1DM undertaken in primary care in the UK, the oral contraceptive pill (OCP) was reported to be the most widely used method of contraception [114]. The combined OCP was used by 17%, and the progesterone-only pill (POP) by 8.6%; however, a more recent survey in general practice in the UK reported women with diabetes were significantly less likely to be prescribed the combined OCP than women without diabetes [116]. In contrast, progesterone-only and depot hormonal contraceptives were relatively more popular in women with diabetes. It seems there is a slight reluctance to prescribe the combined OCP in women with diabetes. The reasons for this are not clear and there are good reasons for using OCP. It is simple to use and, most importantly, very reliable. If properly used, it has the lowest failure rate for any contraceptive method, apart from sterilization [117]. Nevertheless, there have always been concerns about the safety of hormonal contraception in women with diabetes. Both the combined OCP and the POP carry an increased risk of thromboembolic disease and, in theory, can adversely affect glucose metabolism. These concerns are largely unfounded. A systematic review for the Cochrane database reported steroid contraceptive had limited effects of carbohydrate tolerance but strong statements could not be made because of the limited quality of trials [118]. Although a large definitive study examining the effects on cardiovascular morbidity and mortality in women with diabetes has not been performed, several smaller studies have suggested that OCPs with lower doses of estrogen have no greater effect on markers of cardiovascular risk in women with diabetes than women without diabetes [119,120]. Furthermore, there is no evidence that OCPs increase the risk of microvascular complications [121] or worsen metabolic control in women with T1DM [119].

Few studies, if any, have examined the safety of OCPs in T2DM. Two studies have reported that low-dose OCPs have no effect on glucose tolerance or plasma lipids in women with previous gestational diabetes [122,123].

On the available evidence, low-dose (<30 μg estradiol) combined OCPs can be safely used in women with T1DM or T2DM. Any woman taking the OCP should be reviewed regularly for assessment of blood pressure and serum lipids. Women with diabetes can also use the POP. It is not associated with adverse changes in serum lipids or clotting factors and is well tolerated; however, it is associated with menstrual irregularities, particularly intermenstrual bleeding.

Long-acting depot progestin preparations are also effective in women with diabetes. Several small studies have reported that progestins, particularly depot medroxyprogesterone acetate, can worsen carbohydrate tolerance in normal women [124–126], but there is no evidence they have a clinically significant effect on metabolic control in existing diabetes. Depot levonorgestrel (Norplant) appears to have minimal effect on carbohydrate tolerance [125].

Intrauterine contraceptive device

The intrauterine contraceptive device (IUD) is a safe and effective form of contraception in women with diabetes. Early concerns about the risk of pelvic inflammatory disease (PID) in diabetes were largely unfounded; studies have suggested no increased risk of PID in women with T1DM [127] or T2DM [128]. Similarly, early suggestions of an increased failure rate for IUDs in women with diabetes have not been borne out [127].

Barrier methods

Since the advent of AIDS, the condom has been widely advocated to reduce the risk of transmission of sexually transmitted diseases. It has a higher failure rate than OCPs and IUDs and for this reason is not recommended if pregnancy is contraindicated. For high-risk individuals, many genitourinary clinics recommend a combination of the OCP and condom to minimize the risk of pregnancy and sexually transmitted diseases – a technique known as "double-Dutch."

Emergency contraception

Three methods of emergency contraception are licensed in the UK and are available in many other countries: progestogen-only and combined estrogen–progesterone pills, and the copper IUD. The hormonal preparations can be taken up to 72 hours after unprotected intercourse, but are most effective if taken within 24 hours [129]. Nausea was reported in 23% and vomiting in about 6% of the women who used the progesterone-only regimen. Women with T1DM should be warned of these potential side effects. Little work on the use of these agents in women with diabetes has been published, but they may have a role in the prevention of unplanned pregnancies occurring at a time of poor metabolic control.

Conclusions on contraception

All women with diabetes of reproductive age should receive good contraceptive advice, as unplanned pregnancies occurring while glycemic control is poor carry an increased risk of morbidity and fetal abnormalities. Most forms of contraception are safe and effective in women with diabetes, but the OCP remains the most popular as it is very reliable and well tolerated.

Hormone replacement therapy

Attitudes to hormone replacement therapy (HRT) have changed considerably since the start of the new millennium. HRT is well established as an effective treatment for menopausal symptoms and as a treatment for osteoporosis. Until recently there was considerable interest from diabetologists in the potential role of HRT in reducing cardiovascular risk. A survey of general practitioners and hospital doctors in the UK as recently as 2001 suggested the majority would advise HRT for women with diabetes as prophylaxis for cardiovascular disease [130]. This belief was based upon a series of cross-sectional studies and effective marketing by drug companies. Since then the results of a large randomized controlled trials of combined HRT have been published and the results were surprising and interesting. Hulley *et al.* [131] reported that combined HRT did not reduce cardiovascular outcomes in women with established coronary heart disease. The Women's Health Initiative (WHI) study enrolled over 160 000 healthy women and reported in 2002. It was stopped early because of an increase in the risk of breast cancer [132]. Furthermore, there was an significant increase of stroke, coronary heart disease and pulmonary embolus in the group given HRT compared with the control group. There was a reduction in the risk of colorectal cancer and hip fracture. The study also reported an increase in the risk of dementia in the group given HRT [133]. Interestingly, women who took HRT in the WHI had a lower risk of developing diabetes.

Not surprisingly, the WHI study has generated considerable debate and has had a significant impact on practice. Many new guidelines on HRT have been produced, but few in diabetes. A detailed discussion of the benefits of HRT is beyond the scope of this book. The current views of the risks and benefits of HRT are listed in Table 45.8. In brief, in women with diabetes, HRT should be considered for short-term relief of menopausal symptoms, such as hot flushes, but is not indicated for cardiovascular risk reduction.

HRT and glucose tolerance

There is reasonable evidence that HRT does not worsen glucose tolerance in women either with or without diabetes and may produce a slight amelioration. In women without diabetes,

Table 45.8 Risks and benefits of hormone replacement therapy (HRT).

Main benefits of HRT

HRT produces:

- Relief of hot flushes
- Relief of urogenital symptoms
- Reduction of risk of osteoporotic fractures
- Reduction of risk of colorectal cancer

Main risks of HRT

HRT increases the risk of:

- Thromboembolic disease
- Stroke
- Breast cancer (combined HRT)
- Endometrial cancer (estrogen-only HRT)
- Ovarian cancer (estrogen-only HRT)

No change in risk

- Weight gain, headache
- Migraine
- Breast cancer (estrogen-only HRT)
- Colorectal cancer (estrogen-only HRT)

Insufficient evidence

There is incomplete evidence but HRT may worsen:

- Coronary artery disease
- Dementia

estradiol [134] and low-dose conjugated estrogens [135] are associated with an improvement and no effect on insulin sensitivity, while higher doses of conjugated estrogens and alkylated estrogens may cause deterioration of glucose tolerance [134,136–138].

In postmenopausal women with diabetes, estradiol has been reported to improve the fasting blood glucose concentration and glycosylated hemoglobin percentage [139]. A larger prospective study of over 15 000 women with T2DM also reported HRT produced an improvement in HbA_{1c} levels [140]. A recent small randomized trial reported HRT reduced serum fructosamine levels by 5% [141]. Any potential benefit to glucose tolerance is limited to oral HRT preparations: transdermal estradiol does not appear to have any effect on glucose tolerance [142,143].

HRT and lipids

There is now evidence that the effect of HRT on lipid profiles, such as glucose tolerance, is at worst neutral and may be slightly beneficial. In women without diabetes, estrogens reduce total and low density lipoprotein (LDL) cholesterol and increase high density lipoprotein (HDL) cholesterol and triglyceride levels [131,143]. Progestins can reduce triglyceride levels and when given in combination can prevent the estrogen-induced increase. Transdermal estrogen preparations have a beneficial effect on plasma lipids, reducing LDL cholesterol and triglycerides and increasing HDL cholesterol [144].

The effect of HRT on lipid profiles in women with diabetes has been reported to be largely favorable in several studies. In a small randomized cross-over study of overweight women with T2DM, conjugated estrogen therapy reduced central obesity, HbA_{1c} and total cholesterol, and improved physical functioning [145]. In a largert study, 61 postmenopausal women received combined HRT in a randomized cross-over design. HRT reduced total and LDL cholesterol, but there was no change in serum HDL or triglyceride levels [141].

HRT and blood pressure

HRT can be prescribed to hypertensive postmenopausal women under careful supervision. One of the few studies of HRT and blood pressure in diabetes suggested that it can be prescribed without any adverse effect on ambulatory blood pressure measurements in hypertensive and normotensive women [146].

HRT and osteoporosis

There is limited evidence to suggest women with T1DM have reduced bone mineral density at the time of diagnosis [147]. Although women with T2DM might be expected to be protected from osteoporosis because of their increased tendency to obesity, they would appear to be at increased risk of hip fracture (see Chapter 48). A very large prospective cohort study of postmenopausal women in Iowa reported that women with diabetes had a 1.7-fold higher risk of hip fracture than women without diabetes [148]. Thus, the benefits of HRT in reducing the risk of osteoporotic fractures would appear to be at least as great in women with diabetes as women without diabetes. Although HRT can be considered in all postmenopausal women with diabetes and osteoporosis, there are several alternatives including bisphosphonates, raloxifen and strontium which do not have the risks of HRT.

Conclusions on HRT

HRT is an established treatment for the symptoms of the menopause. It is also effective in preventing osteoporosis. It has no adverse effects on glycemic control or lipid profiles. The benefits of HRT do not justify the risks in asymptomatic women and it is not indicated for cardiovascular risk reduction. It can be considered for treating menopausal symptoms in women with diabetes on a short-term basis.

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