Prelox® for Improvement of Erectile Quality

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Abstract

Sexual desire typically persists when men grow older although their ability to attain and maintain erections sufficient to permit satisfactory sexual intercourse gradually declines. Decreasing erectile quality is a common age-related problem affecting the lives of both men and their partners. Lifestyle plays an important role in the onset of erectile quality problems, and timely improvements such as a healthier diet and exercise may significantly slow the progression to erectile dysfunction with increasing age. Essentially, all cardiovascular risk factors – including hypertension, dyslipidaemia, hyperglycaemia, obesity and cigarette smoking – impair endothelial function, which in turn directly translates into declining erectile function. In this regard a man's penis does indeed represent a barometer indicating his cardiovascular health status. Once endothelial function has declined to a point where its restoration is not feasible, pharmacological interventions with phosphodiesterase-5 (PDE5) inhibitors may temporarily bypass physiological processes so that affected men may still enjoy sexual intercourse. A timely intervention that helps to restore endothelial function will have the advantage of preserving a man's ability to spontaneously respond to sexual arousal. Prelox®, a patented complex formulation consisting of Pycnogenol® and L-arginine aspartate, has been demonstrated in four clinical trials to naturally restore healthy erectile quality in men presenting with moderate erectile problems. Pycnogenol, a key component of Prelox, was shown in human pharmacological studies to act as a catalyst on endothelial nitric oxide (NO) synthase for amplified synthesis of NO, the initial mediator for triggering an erection. Its combination with the enzyme's substrate, L-arginine, synergistically increases synthesis of NO, the key component involved in vasodilatation for improved blood flow to engorge the penis. According to reviewed clinical trials, Prelox will help men with moderate erectile problems to regain healthy erectile function, greater confidence to initiate and sustain erections and more frequent morning erections. As a result of higher intercourse frequency, men taking Prelox developed significantly higher plasma testosterone values. Prelox is a safe, well-tolerated and efficacious treatment for mild to moderate cases of declining erectile quality.

Keywords

Erectile dysfunction, Prelox, L-arginine, erection problems, endothelial health

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During the past two decades there has been a dramatic increase in our understanding of the physiology of an erection, as well as of the pathophysiology involved in the decline of erectile function. Men may suffer from erectile dysfunction (ED) as a result of psychogenic factors, such as performance anxiety. Less common are endocrinological influences resulting from cases of hypogonadism or hyperprolactinaemia.

Observational and epidemiological evidence in recent years has increasingly demonstrated a link between ED and typical cardiovascular risk factors. Vasculopathy is now recognised as the most common cause of organic ED. The role of the vascular system is noteworthy as it is today generally accepted that impaired erectile function results from disturbances of the vascular endothelium. This impairment of endothelial function typically develops from vasculopathies such as hypertension, dyslipidaemia, hyperglycaemia and cigarette smoking.[1] Indeed, ED is considered one of the earliest manifestations of vascular disease. This fact has led authors to consider the penis as a 'barometer' indicating endothelial health status.[2] A man presenting with impaired erectile function will be suspected of vasculopathy until proved otherwise. Attempts at a healthier lifestyle involving diet, exercise, suitable supplements and stress reduction have been argued to preserve healthy sexual function and even improve erectile quality.[3] Decreasing erectile quality with increasing age is not a fate men have to live with. From the point of gradual declining erectile quality to the stage where prescribed medication is required for compensation of insufficient physiological function is a long stretch.

Physiology of an Erection

A penile erection is a transformation of penile tissue and vasculature from a state of minimally perfused flaccidity into an engorged state. Following erotic stimulation (visual, auditory, tactile or imaginary), parasympathetic nerves transmit impulses to the cavernous body of the penis. There the parasympathetic nerve fibres divide into two different types of nerve terminal: cholinergic terminals and non-adrenergic, non-cholinergic (NANC) terminals. The cholinergic nerve ends release acetylcholine, which stimulates endothelial nitric oxide synthase (eNOS) for enhanced synthesis of vascular nitric oxide (NO) from L-arginine and O_2, while the NANC terminals predominantly

release neuronal NO from neuronal NOS (nNOS). Within the smooth-muscle cells of arteries the NO activates guanylate cyclase, which catalyses the breakdown of guanosine triphosphate (GTP) into 3'5'-cyclic guanosine monophosphate (cGMP).

cGMP plays a key role as second messenger for releasing smooth-muscle constriction and increasing arterial blood flow to engorge the penis. This is facilitated by activation of protein kinase G for phosphorylation of potassium channels, causing K^+ outflow and, subsequently, decreased intracellular Ca^{2+}. Physiologically, intracellular Ca^{2+} regulates cavernous capillary smooth-muscle constriction to maintain flaccidity. The depletion of smooth-muscle Ca^{2+} lowers actin–myosin interaction (relaxation) and, consequently, leads to vasodilatation. This process is counteracted by the enzyme phosphodiesterase (PDE), which breaks down cGMP into inactive 5' guanosine monophosphate (5-GMP). There are several PDE isoforms present in the corpus cavernosum, with PDE5 being the most abundant.[4] While the impaired ability of the endothelium to generate sufficient quantities of NO represents the pathophysiological reason for men's declining erectile quality, the temporary inhibition of PDE5 represents the pharmacological leverage for its compensation. An attempt to reinstate healthy endothelial function would help restore natural erectile function.

Prelox®

Pharmacology and Rationale

Prelox® is a registered trademark of Horphag Research Ltd for a patented proprietary blend of French maritime pine extract Pycnogenol® and L-arginine aspartate (US patent 6,565,851 B2). Prelox was developed to improve NO synthesis and, consequently, erectile quality in men. An erection vitally depends on the availability of both neuronal and endothelial NO; the nutritional components provided with Prelox facilitate the physiological processes involved.

The amino acid L-arginine plays a key role in vasculature dynamics because it represents the substrate for all NOS isoforms. Arginine supplementation is able to increase NO production despite physiological concentrations exceeding saturation levels of NOS, a phenomenon known as the 'arginine paradox'.[5] In patients with diagnosed ED, dietary supplementation with L-arginine alone appears to be effective for improving the condition, provided the dosage and intake duration are sufficient. One group in a double-blind, placebo-controlled trial found significant improvements with 5g L-arginine per day over a period of six weeks.[6] Another group found in a double-blind, placebo-controlled, cross-over study that 1.5g L-arginine a day for 17 days was ineffective.[7] Experiments with isolated human corpus cavernosum leave little doubt that L-arginine evokes detectable corpus cavernosum relaxation proportional to concentration and time.[8]

Pycnogenol consists of phenolic substances chemically classified as flavonoids: phenolic acids resembling benzoic acid and cinnamic acid derivatives, taxifolin and procyanidins, condensed catechin and epicatechin moieties of variable chain length (n=2–12).[9] Pycnogenol is standardized to contain 65±5% procyanidins, as detailed in the *United States Pharmacopoeia*.[10] Human pharmacological studies have demonstrated that Pycnogenol stimulates endothelium-dependant vasodilatation in a double-blind, randomised, placebo- and active-drug-controlled study.[11] Healthy students consuming Pycnogenol over a period of two weeks showed a faster and more pronounced relaxation of forearm arteries, measured by forearm blood flow by means of plethysmography, in response to infusion of increasing amounts of acetylcholine. Corresponding controls employing administration of NG–monomethyl–L-arginine, an eNOS inhibitor, completely abolished the Pycnogenol-induced augmented forearm blood flow response to acetylcholine. These investigations in healthy volunteers conform to earlier studies carried out in isolated arteries *ex vivo*.[12] The exact molecular effects of Pycnogenol and its metabolites on eNOS are the subject of extensive investigation. In theory, antioxidants may extend the half-life of NO by preventing the oxidation of NO to inactive nitrite and nitrate.[13] This possibility was ruled out in experiments with isolated aortic rings *ex vivo*, where the presence of superoxide dismutase significantly altered Pycnogenol-induced vasorelaxation.[12] The acute release of aortic constriction, induced by adrenaline or noradrenaline (epinephrine or norepinephrine), within 10 minutes after Pycnogenol presence suggests a catalytic activity on eNOS for enhanced NO synthesis. However, current *in vitro* investigations of possible mechanisms of Pycnogenol effects point to an upregulation of NOS expression (Petra Högger, University of Würzburg, Germany; personal communication). Detailed investigations of the molecular interactions of Pycnogenol–L-arginine combinations related to synergetic activities for NO synthesis are currently ongoing.

Synergistic effects of the enzyme substrate L-arginine and Pycnogenol catalytic activity for eNOS are indeed expected to significantly elevate NO synthesis. While the detail of what happens on a cellular level should be revealed in the near future, exploratory human studies have demonstrated a synergistic effect of Pycnogenol and L-arginine aspartate for increased eNOS activity in sperm lysate.[14] Sperm specimens were collected from men with moderate ED participating in a clinical trial before and after treatment with Prelox. Spermatozoa bear an NOS isoform whose activity can be measured subsequent to lysation by quantification of L-citrulline.[15] After Prelox consumption, sperm lysates synthesised almost twice as much citrulline as sperm lysates from the same men before they took Prelox. The limitation of this experiment is that it offered only circumstantial evidence for increased NO synthesis, as it was demonstrated in other tissue.

History of Development

A pilot trial investigated the effect of Pycnogenol in 21 subjects presenting with moderately high total cholesterol (average 5.41mmol/l) and mild to moderate ED as judged by the erectile domain of the International Index of Erectile Function (IIEF-5).[16] The daily consumption of 120mg Pycnogenol steadily increased men's IIEF-5 score from one month to another. Starting from a baseline of 12.6/25, the values reached 13.8, 14.6 and 16.8 following one, two and three months of treatment, respectively.[17] Erectile function values improved from 'moderate' to 'mild' ED after three months, and at this time reached statistical significance compared with a placebo-treated group. After discontinuation for one month the IIEF score decreased again to 14.5. This study showed that Pycnogenol alone may improve erectile quality, most likely due to improved endothelial function, provided the treatment duration is sufficient.

The validation of the concept of Prelox displaying synergistic effects of Pycnogenol and L-arginine aspartate was shown by testing the components individually and then acting in concert[18] in a group of 40 men with confirmed functional ED to the extent that they were unable to achieve adequate erections sufficient for vaginal penetration or completion of successful intercourse. For a period of one month, they were given a daily dosage of 3g L-arginine aspartate, which corresponds

Figure 1: Double-blind, Placebo-controlled Cross-over Study with Prelox

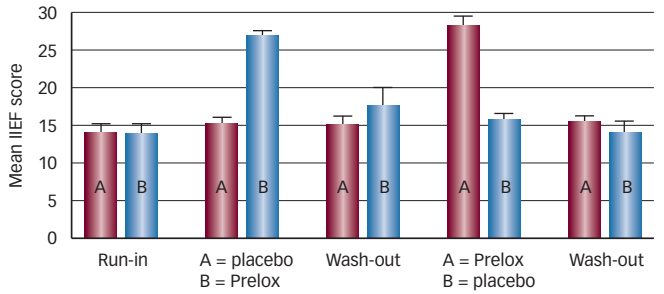
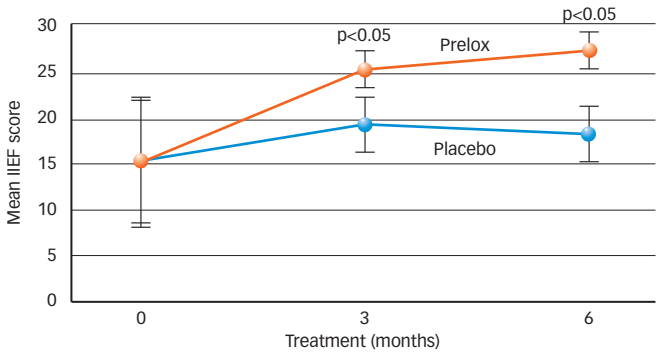


Figure 2: Six-month Double-blind, Placebo-controlled Study with 124 Men



to 1.71g L-arginine. This enabled only two of the patients (5%) to regain erectile function sufficient for sexual intercourse. During the following month all men continued the amino acid regimen, and additionally took 80mg Pycnogenol per day. The success rate was dramatically increased, with 32 men (80%) regaining erectile function. For the subsequent month, amino acid supplementation was maintained and 120mg Pycnogenol a day was taken. The increased daily intake of Pycnogenol by 50% a day increased the number of men with restored erectile function to 38 (92.5%). The outcome of the study clearly suggests that the majority of the effect on men's erectile function resulted from the combination of Pycnogenol with L-arginine aspartate, because the increased dosage of Pycnogenol by 50% yielded only a 12.5% increased success rate. Furthermore, compared with the initial ED study with Pycnogenol only, which found significant improvement only after three months, the combination of Pycnogenol with the amino acids resulted in significant effects after one month. It may be speculated that the further increase in the number of men with restored erectile function after treatment with a higher Pycnogenol-to-L-arginine ratio simply resulted from an additional month's treatment rather than reflecting any dose effects.

From the two exploratory studies, the Prelox formulation was established to contain 20mg Pycnogenol and 700–750mg L-arginine aspartate. Compositions with higher dosages are not feasible because of technical (tablet size) limitations.

Efficacy

The efficacy of Prelox was validated in a clinical investigation in 40 men presenting with mild to moderate forms of ED who had no previous experience with PDE5 inhibitors.[19] A daily dosage of four Prelox tablets was taken over a period of six weeks. Analysis of the erectile function domain of the IIEF (questions 1–5 and 15) showed a statistically significant increase from a baseline average of 22.1 to 24.5 after six weeks of taking Prelox. Closer examination showed that Prelox was more effective for men who presented with higher IIEF scores at baseline than those with lower initial values. In this study a further examination related to men's sexual quality of life was carried out. The authors found that the majority of men experienced an easier initiation of erections during arousal and found it easier to sustain their erections. Furthermore, 65% of the men reported increased morning erections after taking Prelox for six weeks.

A double-blind, placebo-controlled, cross-over study with 50 men further established the efficacy of Prelox for improvement of erectile quality.[14] Only men with a stable sexual partnership during the past six months and with moderate ED corresponding to values ranging from 11 to 17 on the erectile function domain of the IIEF score (questions 1–5 and 15; score range 0–30) were recruited for this study. They had no previous experience with PDE5 inhibitors and did not take any prescribed medications during the trial period. These men presented with moderate cardiovascular risk factors related to bodyweight (average body mass index [BMI] 26.05kgm^{-2}) and blood pressure (BP) (average systolic BP 133.5mmHg). Men were randomly assigned to one of two groups, A and B, with 25 men in each group. The two groups did not significantly differ in terms of baseline IIEF scores and mean intercourse frequency (average 4.5 per month).

Figure 1 illustrates the chronology of the study protocol comprising the five-month investigation period. During the first month (run-in period) baseline IIEF scores were recorded. During the second month, group A was given placebo, while group B received four Prelox tablets, which led to a substantial increase of IIEF scores. The third month served as a wash-out period, after which the IIEF scores in the previously Prelox-treated group returned to almost baseline values. In the fourth month group A was given Prelox, which led to significantly higher IIEF scores, while group B with placebo showed no effect. During the fifth month no supplementation took place, and during this period the IIEF scores in group A dropped to baseline values.

Following the treatment of respective groups with Prelox, men reported a significantly increased frequency of morning erections and easier initiation of and more sustained erections. Also, their partners noted improved performance. Following the one-month consumption of Prelox, the plasma testosterone level increased significantly from 17.5 to 22.2nmol/l ($p<0.02$) in group A and from 18.1 to 22.0nmol/l ($p<0.001$) in group B. The investigators argued that the increased testosterone level would be a secondary effect of the increased intercourse frequency of patients, which is known to be associated with increasing testosterone.[20] Indeed, the mean intercourse frequency more than doubled during treatment from 4.4 to 10.7 and from 4.6 to 11.2 per month, respectively.

Another double-blind, placebo-controlled Prelox product evaluation study was carried out in 124 men (average age 44 years) presenting with moderate ED.[21] Men in stable partnerships for at least six months presenting with moderate ED were enrolled. Patients were randomly assigned to either four Prelox tablets (two in the morning, two in the evening) or corresponding placebo tablets over a period of six months. Fasting blood samples were taken at baseline and following completion of the trial for standard blood chemistry and rheology.

Thirteen men dropped out due to non-medical reasons. In the Prelox group, the average IIEF score increased from a baseline of 15±6.6 to 25±2 after six months of treatment. The placebo group started with an

average score of 15±7, which increased to 19±3 at trial end. The improved erectile quality in the Prelox group was statistically significant compared with the placebo group ($p<0.05$) (see *Figure 2*). More men in the Prelox group than in the control group reported increased morning erections (36 versus 12%), easier to initiate erections (38 versus 12%), partner noticing increased interest (38 versus 6%) and partner noticing improved performance (38 versus 12%). Many men were uneasy about responding to the above questions.

Blood chemistry and rheology found no major changes after six months of Prelox or placebo intake. A non-significant decrease of systolic blood pressure from a baseline average of 138.9 to 131.0mmHg was found in the Prelox group. A statistically significant increase of plasma testosterone was evident in the Prelox group, from a baseline of 458 to 544ng/dl after six months, representing an increase of 18.8%.

Duration of Action

In principle, the activity of Prelox is directed towards restoring endothelial function, which will allow men to spontaneously respond to sexual arousal. How quickly a man experiences an improvement of erectile quality will depend on his individual situation. From the clinical trial of Stanislavov et al., information is available on the earliest effects of erectile quality.[14] This was reported to be as early as one day after taking four Prelox tablets, with the latest response reportedly after nine days; the mean response occurred after 4.9 days. This trial also showed that following discontinuation of Prelox for one month, erectile quality decreases to almost pre-treatment levels.

An important point to consider is whether a habituation effect may occur after continuous supplementation with Prelox, with the effect on erectile quality gradually fading with time. The study by Ledda et al. provides information that this does not occur; in fact, the contrary is true.[21] A comparison of IIEF scores after three months on Prelox with scores after six months clearly shows that erectile quality further improves following an additional three months of treatment. Therefore, in order to achieve the best effects Prelox would need to be taken continuously, without interruption.

Dosing and Absorption

In all clinical investigations for improvement of erectile quality, a daily dosage of four Prelox tablets was taken. In one study the equivalent of six Prelox tablets was taken for one month. The ideal initial dosage would thus be four Prelox tablets a day: two in the morning after breakfast and another two after dinner. Once erectile quality has sufficiently improved, the dosage may be adjusted to a maintenance dosage, which could be three or two Prelox tablets a day. The suitable maintenance dose will depend on a man's individual condition.

Metabolism and Excretion

Dietary L-arginine is absorbed in the small intestine via a specific amino acid transport system. About 60% of the absorbed L-arginine is metabolised by gastrointestinal enterocytes, while only 40% reaches the systemic circulation intact.[5] The average dietary consumption of L-arginine is about 5g/day. L-arginine undergoes various metabolic fates: much is converted to NO and L-citrulline, the latter being largely converted in the proximal renal tubule to L-arginine. Furthermore, L-arginine may be utilised for protein synthesis or converted into other amino acids such L-ornithine, L-proline and L-glutamate. L-arginine is an alkaline amino acid that is not very water-soluble, unless in ionic forms with anionic countercharge; aspartate fulfils this purpose in Prelox.

The pharmacokinetics and excretion of Pycnogenol were shown to be of complicated nature in humans. The smaller flavonoid constituents, namely the phenolic acids and catechin, are found in blood plasma of humans within 30 minutes after oral consumption.[22] These constituents are excreted in the urine as sulphates and glucuronates, with peak times about two hours post-consumption.[23] The procyanidins are metabolised in the colon prior to absorption into the blood stream. Specifically, the metabolite δ-(3,4-diydroxy-phenyl)-γ-valerolactone was identified in the plasma beginning four hours after consumption, and appears in the urine at peak eight to 10 hours post-consumption. Several further metabolites can be found in the plasma of humans that have so far not been identified in the urine.

Adverse Effects

In all four clinical trials Prelox was well tolerated and no side effects occurred. Prelox has been marketed in the US and in European countries since 2004. Post-marketing surveys have resulted in a collection of consumer self-reported side effects directly to the corresponding marketing companies. The following unwanted effects were self-reported: dizziness (n=2), nausea (n=1), vertigo (n=1), headache (n=1), diarrhoea (n=1), worsened tinnitus symptoms (n=1), feeling sick (n=1) and hypotension (n=1). In all cases it was advised to immediately discontinue the supplementation. It was not possible in these cases to verify the nature and circumstances of the self-reported side effects. Likely only a small percentage of men will report their side effects to the manufacturer or the website (www.Prelox.com). However, in view of the considerable quantities of Prelox sold during the past five years, the number of unwanted side effects appears to be fairly low and is in concordance with the experience from clinical trials.

Safety and Drug Interactions

Pycnogenol acute oral toxicity is very low, with a demonstrated no observed adverse effect level (NOAEL) of 150mg/kg.[9] Pycnogenol itself is known to cause stomach discomfort in some particularly sensitive people because of the pronounced astringency of the procyanidins. This happens only when Pycnogenol is taken on an empty stomach. Interestingly, stomach discomfort has not been reported for Prelox. A possible explanation is that the considerable amount of amino acids helps to avoid the stomach discomfort.

There is some dispute as to possible harm from L-arginine in people suffering from herpes. As early as the 1960s it was found that L-arginine promotes replication of herpes simplex in tissue culture, while L-lysin inhibits replication. The authors concluded: "the *in vitro* data may be the basis for the observation that patients prone to herpetic lesions and other related viral infections, particularly during periods of stress, should abstain from arginine excess and may also require supplemental lysine in their diet".[24] Whereas L-lysin indeed appears to offer prophylactic activity for managing recurrent herpes outbreaks in humans,[25] more recent studies suggest that L-arginine has antiviral effects against herpes simplex.[26]

A further unsubstantiated possible side effect of L-arginine is the promotion of tumour growth. One group has described higher protein synthesis in breast tumours as a result of supplementation with L-arginine.[27] The same group later argued that dietary supplementation with L-arginine would offer adjuvant treatment for improved host defence in breast cancer patients as a result of immunostimulatory effects.[28] The work of this group has left

considerable confusion, with various publications on L-arginine in cancer patients with contradictory findings.

However, men who have suffered a myocardial infarction should definitely refrain from taking Prelox because L-arginine may pose a health risk to them.[29] One study investigated supplementation with accelerating dosages of L-arginine, from 3 to 9g daily, for improving vascular stiffness and heart ejection fraction in addition to standard post-infarction therapy. The study was prematurely terminated after six months because of safety concerns, as six patients (8.6%) taking L-arginine died, whereas none in the placebo group did. Interestingly, after six months the L-arginine plasma levels were not significantly different between the treatment and placebo groups. The authors state "the excess mortality was an unexpected safety monitoring concern and the results could be due to (small but nonzero) chance". Schulman et al. conclude that L-arginine therapy should not be given to patients following myocardial infarction.

Prelox has not been systematically investigated for specific drug interactions. From the pharmacological activities of Prelox it may be concluded that for certain medications the attention of the treating physician is mandatory. Men diagnosed with angina pectoris on medication with 'nitrates' (i.e. glycerol nitrate, isosorbide dinitrate, isosorbide mononitrate) should supplement with Prelox only with the consent of their physician.

Prelox was shown in two trials to lower blood pressure, although not to the point of hypotension.[14,20] Therefore, caution should be exercised in men medicating with antihypertensive medications. The guidance of a physician is advised as the hypertensive medication dosage might require adjustment. Men taking oral anticoagulants such as warfarin should supplement with Prelox only under the supervision of a physician, as the improved endothelial function and nitric oxide synthesis naturally lower platelet activity. The latter effect should be minimal compared with the potency of warfarin, but caution is advised.

The safety of supplementing with Prelox and co-medicating with PDE5 inhibitors needs to be addressed as a potential synergistic effect may also generate advanced side effects. Limited knowledge is available on the simultaneous use of Prelox and PDE5 inhibitors. An exploratory investigation tested co-medication in men >50 years of age presenting with moderate to severe ED who took four Prelox tablets a day and 50mg Viagra® twice a month 30 minutes prior to intercourse (Margus Punab, Tartu Men's Clinic Finland; personal communication). The results were judged 'good' and, more importantly, no side effects were reported with the combination.

Conclusion

Prelox is a safe, well-tolerated and efficacious treatment for mild to moderate aetiologies of ED. Its efficacy has been proved in four clinical trials. The unique characteristic of Prelox is the restoration of men's ability to spontaneously respond to sexual arousal. Prelox is a treatment option for ageing men who discover the first signs of decreasing erectile quality. Studies show that men taking Prelox are more confident and more frequently have intercourse. This is a protective measure for developing ED, as found in an epidemiological study. Men who have intercourse more frequently are less likely to develop ED later in life.[30] ■

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