Chapter 3
Medical and Lifestyle Approaches to Improving Semen Quality

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Clinical Vignette

Mr. PM, a 35-year-old male and his 32-year-old G0P0 female partner complain of the inability to conceive after 15 months of unprotected intercourse. His past medical and surgical histories are noncontributory. He is an active smoker with a smoking history of one pack per day for 20 years, and he drinks two–three beers every day. His physical examination is unremarkable. The fertility workup of his female partner is normal. His laboratory values are given in Tables 3.1 and 3.2.

Lifestyle Approaches to Improving Semen Quality

There has been a dramatic change in the factors that are potentially associated with alterations in semen quality over the past several decades. For example, there has been a marked increase in the consumption of substances of abuse [1] and the population of smokers [2] worldwide. Centola et al. [3] have demonstrated a significant decline in semen parameters such as sperm concentration (−3.55 million/mL/year, 95% CI −4.87, −2.23; $p < 0.001$), total motility (−1.23%/year, 95% CI −1.65, −0.82; $p < 0.001$), total sperm count (−10.75 million/year, 95% CI −15.95, −5.54; $p < 0.001$), and total motile count (−9.43 million/year, 95% CI −13.14, −5.73; $p < 0.001$) in young adult men over a period of 10 years between

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Table 3.1 Case study laboratory values

Test	Value	Reference range
FSH (mIU/mL)	4	4–10
LH (mIU/mL)	5	4–12
Testosterone[a] (ng/dL)	198	250–1000
Estrogen (pg/mL)	25	10–40
Prolactin (ng/mL)	10	2–18

[a]Drawn on two separate occasions before 10 AM

Table 3.2 Case study semen analysis

Semen analysis (average of 2 separate analyses)		
Concentration	8 million/mL	$\geq$ 15 million/mL
Motility	30%	$\geq$ 50% motility

Table 3.3 Impact of lifestyle factors on seminal parameters

Lifestyle factor	Duration/intensity	Impact on seminal parameters
Smoking	$\geq$ 10 years or $\geq$ 20 cigarettes/day	Impaired sperm DNA integrity, nuclear maturation
Alcohol consumption	$\geq$ 8 alcoholic drinks/week	Impaired spermatogenesis, teratospermia
Exogenous testosterone/anabolic steroids	–	Impaired spermatogenesis

2003 and 2013. This part of the chapter outlines the effects that certain lifestyle factors such as smoking, alcohol consumption, and use of anabolic steroids may have on semen quality and male fertility (Table 3.3).

Smoking

The number of smokers has grown to include nearly one-third of the global population above the age of 15 years [2], despite growing evidence of the deleterious impact of smoking on nearly every organ in the human body. Smoking is associated with male subfertility [2]. Although the exact mechanisms through which smoking impacts male fertility are presently unknown, several theories have been proposed, a couple of which include the reduced delivery of oxygen to the testes that compromises the high metabolic requirements of spermatogenesis, and the oxidative stress conferred by several metabolites of cigarette smoke (tar, benzopyrene, carbon monoxide, aromatic hydrocarbons) [2, 4, 5].

In a large meta-analysis of 57 studies, Li et al. [6] reported that smoking is associated with deterioration of multiple semen parameters such as total sperm count, sperm volume, sperm density, sperm morphology, and progressive sperm motility, both in fertile and infertile men. These results were consistent with the results of another meta-analysis that demonstrated an association between smoking and a reduction in sperm density and sperm motility [7].

In addition to semen parameters, the detrimental impact of smoking on male infertility is compounded by its association with a reduction in seminal zinc (a key antioxidant) levels, sperm vitality, and sperm DNA integrity, and an increase in semen reactive oxygen species. A review of 160 fertile men concluded that fertile smokers showed a significantly higher sperm DNA fragmentation percentage and seminal reactive oxygen species levels, as well as a significantly lower progressive sperm motility, hypo-osmotic swelling test percentage, and seminal zinc levels compared to fertile nonsmokers [8]. Moreover, the quantity and duration of smoking were both positively correlated with sperm DNA fragmentation percentage and seminal reactive oxygen species, and negatively correlated with sperm motility, seminal zinc levels, sperm count, and the percentage of morphologically normal sperm. Furthermore, it has been shown that smoking for more than 10 years or greater than 20 cigarettes/day has a deleterious impact on sperm DNA integrity and nuclear maturation [9]. Sperm fertilizing capacity, as assessed by the zona-free hamster oocyte sperm penetration assay, has also been shown to be markedly reduced in smokers as compared to nonsmokers [10].

A clear understanding of the pathophysiologic mechanisms through which smoking negatively effects semen quality and male fertility notwithstanding, the current scientific literature strongly shows that it significantly impairs male reproductive potential.

In light of his long and heavy smoking history as presented in the aforementioned clinical vignette, Mr. PM should be advised to quit smoking, not just as a critical part of improving his fertility potential, but also because of its deleterious impact on other organ systems such as cardiovascular morbidity and tumorigenesis. He should also be counseled that the detrimental effects of smoking on semen quality have been shown to be reversible with smoking cessation. Santos et al. [11] showed that smoking cessation for 3 months led to an increase in sperm count (72 million vs. 29 million/ejaculate), sperm vitality (20% vs. 60% necrotized), sperm motility (79% vs. 33%), and the number of grade A spermatozoa recovered after swim-up (23 million vs. 3 million/ejaculate).

Alcohol

Alcohol has been shown to have a detrimental impact on male fertility at all levels of the male reproductive system [12]. It compromises the regulation of the hypothalamic–pituitary–testicular (HPT) axis, thereby resulting in a reduction of

luteinizing hormone (LH) and follicle stimulating hormone (FSH) production [13, 14], and the subsequent impairment of spermatogenesis [15].

A study showed that only 12% of the men that consumed alcohol had normozoospermia, as compared to a control group of nonusers in whom the rate of normozoospermia was 37% [16]. Close et al. [17] analyzed the semen parameters of 164 men and concluded that the seminal fluid leukocyte concentration was significantly higher in chronic alcohol users as compared to nonusers. However, after controlling for a past history of sexually transmitted diseases and exposure to multiple substances of abuse, there was only a trend of higher leukocyte count in alcohol users. Consumption of more than eight alcoholic drinks per week has been shown to be associated with male subfertility, with the most common semen parameter anomaly of teratospermia [4]. Additionally, consuming more than 40 grams of alcohol per day showed an increase in spermatogenic disorders [18]. Not only chronic consumption, but even excessive acute alcoholic binges have been shown to be associated with worse semen parameters and an increase in the free estradiol/free testosterone (E2/T) ratio in a cross-sectional study including 347 men [19].

Despite multiple studies investigating the topic, the threshold of quantity at which alcohol consumption negatively affects semen parameters is not well defined. However, it can be inferred from the current scientific literature that consuming more than eight alcoholic drinks per week is detrimental to semen quality [4].

In our clinical vignette, the current average alcohol consumption of Mr. PM is 17–18 drinks—more than twice the upper limit of consumption that is detrimental to male fertility. He should be strongly counseled to reduce his alcohol intake to help restore his fertility.

Exogenous Testosterone and Anabolic Steroids Abuse

There has been a 90% increase in the number of testosterone prescriptions and more than a threefold increase in the use of testosterone replacement therapy (TRT) in men over the past 15 years [20, 21]. In the USA, the rate of TRT has been rising since 2000, but has seen an especially steep increase since 2008 [20]. Furthermore, recent trends suggest that TRT is being prescribed to a significant number of men still in their reproductive years [22].

Exogenous testosterone decreases the levels of FSH, LH, and intratesticular testosterone and impairs spermatogenesis by suppressing the HPT axis [23]. This effect seems to be considerably stronger with intramuscular testosterone as compared to topical formulations [24]. One of the reasons for the high prevalence of testosterone use in infertile men of reproductive age despite its contraceptive effects is the misconception that it enhances fertility—a notion not just limited to patients, but a high percentage of urologists who have indicated that they would use testosterone for the empirical treatment of male infertility [24].

Since it can lead to the atrophy of germinal epithelium, exogenous testosterone may impair spermatogenesis and cause azoospermia within 10 weeks after

initiation of TRT [25]. However, most men are able to regain the baseline spermatogenic function after cessation of TRT [26, 27]. The largest study on the topic that involved men receiving intramuscular TRT for a period of 30 months showed that the median time to recovery for baseline spermatogenesis prior to TRT was 6 months, with more than 99% of the men regaining their baseline spermatogenesis by 15 months [26]. Another integrated analysis of 30 studies evaluated the recovery of spermatogenesis after TRT used as hormonal male contraception, and showed that 90, 96, and 100% of men were producing sperm with a concentration ≥ 20 million/mL by 12 months, 16 months, and 24 months after TRT cessation, respectively [27]. The current scientific evidence clearly shows that most men of reproductive age receiving TRT for treatment of hypogonadism will experience the resolution of their azoospermia or severe oligospermia within 4–12 months after cessation of TRT [28].

Anabolic steroid abuse (without prescription) among men is another significant and underreported issue associated with male infertility, with a lifetime prevalence between 3.0 and 4.2% [1]. Similar to testosterone, anabolic steroids exert a negative feedback effect on the hypothalamus and pituitary glands, thereby suppressing the release of LH and FSH [29] and decreasing the production of endogenous testosterone and spermatogenesis. The deterioration of semen quality after anabolic steroid abuse mainly presents in the form of oligospermia, azoospermia, sperm dysmorphia, and dysmotility [30, 31]. However, most cases of anabolic steroid-induced infertility are also reversible, and usually resolve within 4–12 months after discontinuation of use [32].

Medical Approaches to Improving Semen Quality

Medical treatment is primarily effective in the treatment of secondary testicular failure as opposed to primary spermatogenic failure due to a lack of clear understanding of the multiple discrete defects that lead to idiopathic spermatogenic failure [33]. This part of the chapter outlines the impact that certain hormonal medications such as anti-estrogens, gonadotropins, and aromatase inhibitors may have in the treatment of male infertility, primarily spermatogenic failure (Table 3.4).

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) such as clomiphene and tamoxifen were the mainstay of treatment for male infertility before the advent of intracytoplasmic sperm injection (ICSI). The mechanism of action of both drugs relies upon their antagonistic activity that blocks the inhibitory feedback exerted by estrogen on the hypothalamus and anterior pituitary, thereby resulting in increased production

Table 3.4 Effects of commonly used medications on seminal parameters

Medication	Effect on seminal parameters
Testosterone	Impaired spermatogenesis
Alpha-blockers	Decreased sperm count and motility
5 alpha-reductase inhibitors	Decreased sperm count in 5% of men
Psychotropic medications	
• Tricyclic antidepressants	Decreased sperm volume and motility
• Lithium	Decreased sperm viability
Anti-hypertensive medications	
• Beta-blockers	Impaired sperm motility
• Diuretics	Decreased sperm concentration and motility
• Calcium channel blockers	Decreased sperm density, motility, and acrosome reaction
Antibiotics	
• Nitrofurantoin	Decreased sperm count at high doses and spermatogenic arrest
• Macrolides	Asthenospermia or sperm death at high doses
• Aminoglycosides	Adversely affect spermatogenesis
Anticancer medications	
• Chemotherapeutic agents	Damage to spermatogonial stem cells and Sertoli cells

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of pituitary gonadotropins (FSH and LH) that stimulates spermatogenesis and production of testosterone by testes. Their favorable side effect profile, ease of administration, and low cost makes them viable treatment options.

Unfortunately, the efficacy of anti-estrogens alone has not been established for the treatment of male subfertility since many pertinent clinical trials have used clomiphene and tamoxifen in combination with other agents as the treatment protocol. A randomized controlled trial concluded that in men diagnosed with idiopathic oligoasthenozoospermia, a combination of daily clomiphene (25 mg) and vitamin E (400 mg) led to a significant improvement in total sperm count, forward progressive motility, and unassisted pregnancy rate (37% vs. 13%, $p = 0.04$) when compared to placebo [34]. However, only 30 couples were recruited in each arm of the trial. A meta-analysis of 738 subfertile men with oligoasthenozoospermia that were exposed to short-term anti-estrogen treatment protocols reported only a 2.9% increase in pregnancy rate as compared to the control group (15.4% vs. 12.5%, odds ratio: 1.56; 95% CI 0.99–2.19) [35]. The authors concluded that there is a lack of evidence to support the use of anti-estrogens in the management of oligoasthenozoospermia. In another multi-institutional study by Hussein et al. [36], 64% (27/42) men with non-obstructive azoospermia responded to treatment with clomiphene and produced enough sperm in the ejaculate to be able to undergo ICSI. The dose of clomiphene was titrated to achieve a serum testosterone level between 600 and 800 ng/dL. The posttreatment concentration of sperm ranged between 1 and 16 (mean: 3.8) million/mL. However, the absence of cases of Sertoli-cell-only

syndrome in the studied population and the lack of a control group make it impossible to establish a treatment-related effect of anti-estrogens on fertility outcomes.

Aromatase Inhibitors

Aromatase inhibitors, such as testolactone and anastrozole, increase serum androgen levels by inhibiting the conversion of androgens (testosterone and androstenedione) to estrogens (estradiol and estrone). The mechanism for increased endogenous testosterone relates to the decreased feedback inhibition of estrogens on the pituitary and hypothalamus, leading to greater gonadotropin release [37]. Administration of aromatase inhibitors has been shown to significantly improve semen parameters such as sperm concentration and motility in oligozoospermic men [38]. Most patients that are suitable for therapy with aromatase inhibitors have been shown to have a testosterone-to-epitestosterone (T/E) ratio of <10 [38]. Despite the commercial unavailability of testolactone in the United States, it has been found to be more beneficial than anastrozole for the treatment of subfertile men with Klinefelter syndrome [39].

Gonadotropins

Hypogonadotropic hypogonadism (low FSH, LH, and testosterone) can be idiopathic or have a multitude of other etiologies, such as congenital gonadotropin-releasing hormone (GnRH) deficiency (Kallmann's syndrome), neoplastic (pituitary adenoma, craniopharyngioma, and other central nervous system tumors), or systemic (sarcoidosis, hemochromatosis). Diagnosis and treatment of these underlying conditions with medications, if present, may improve fertility.

Most men with hypogonadotropic hypogonadism benefit from restoration of spermatogenesis with the use of gonadotropin replacement therapy [40]. Although both pulsatile GnRH and gonadotropin therapy appear to be equivalent in improving semen quality and pregnancy rates [41, 42], very few centers use pulsatile GnRH due to the inconvenience caused to patients by having to wear a continuous subcutaneous infusion pump.

The conventional treatment regimen for gonadotropin deficiency involves human chorionic gonadotropin (hCG) as a substitute for LH (1500–2000 IU subcutaneously, twice or thrice per week) with or without recombinant human FSH (rhFSH) (100–150 IU, 2–3 times weekly). The efficacy of this treatment regimen is supported by significant evidence in the literature. In a prospective study, there was an increase in the mean total motile sperm count from zero to 4.8 million, and testicular volume from 4.1 to 12.4 mL [43]. Addition of FSH to hCG is more likely to restore spermatogenesis men with prepubertal onset of hypogonadotropic

hypogonadism, as opposed to men with postpubertal onset in whom hCG alone seems sufficient to produce the desired outcome [44]. Another study of men with hypogonadotropic hypogonadism showed that 81 men achieved normal testosterone concentration but remained azoospermic after pretreatment with hCG, and of these men, 68 (84%) achieved spermatogenesis and 56 (69%) achieved sperm concentration $\geq$15 million/mL after combination therapy with hCG and rhFSH [45]. Another smaller study confirmed the efficacy and tolerance of the combination therapy in 21 azoospermic men with hypogonadotropic hypogonadism [46]. Another multi-institutional, open-label, phase III randomized efficacy and safety study demonstrated that a weekly dose of rhFSH (450 IU), in combination with hCG, successfully induced spermatogenesis in many men with hypogonadotropic azoospermia that initially failed treatment with hCG alone [47]. Time of onset of gonadotropin deficiency and testicular volume are the best predictors of response to gonadotropic therapy [48, 49].

Pulsatile GnRH therapy is typically initiated with a starting dose of 25 ng/kg/pulse administered every 2 h subcutaneously using a portable infusion pump [50]. The dose is adjusted to achieve a mid-normal testosterone level, and a dose of up to 200 ng/kg may be required to induce virilization [50]. The dose can be reduced after the successful appearance of secondary sexual characteristics [50].

There is little evidence to support the use of gonadotropins in men not suffering from hypogonadotropic hypogonadism. In a study that randomized 112 oligoasthenozoospermic men to treatment with 100 U of rhFSH every other day for 3 months versus no treatment, there was no improvement in the seminal parameters of the treated cohort [51]. However, on subgroup analysis, a group of men with cytological evidence of hyperspermatogenesis on fine needle aspiration had a significant improvement in their seminal parameters [51].

Conclusion

This chapter highlights the impact of some of the most common lifestyle and medical factors on sperm quality and male fertility as per existing scientific literature. However, it is very likely that many additional factors that impact sperm quality are yet to be identified and investigated. Further research and well-designed, clinically meaningful studies are required to clearly establish the impact of these factors on sperm quality in order to effectively treat male infertility.

In the case of Mr. PM, he should be strongly counseled to quit smoking and reduce his alcohol consumption. Furthermore, he should undergo comprehensive liver function evaluation, since hepatic disease secondary to chronic alcoholism may cause an increase in serum estrogen levels and affect fertility. His semen analysis should be repeated in 3 months.

Lifestyle areas to consider

1. Occupational hazards (taxi drivers, working in hot environment, use of laptops)
2. Potential impact of cell phone use (microwave)
3. Obesity as a lifestyle issue is widely discussed because of its impact on men's fertility and sexual potency.

Other suggested management approaches

1. Lifestyle modification: clothing, avoiding hot environment, giving up recreational drugs (cannabis, heroin, kata)
2. The role of antioxidants.

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