New insights to guide patient care: the bidirectional relationship between male infertility and male health

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Male reproduction is a complex process, and numerous medical conditions have the potential to alter spermatogenesis. In addition, male factor infertility may be a biomarker for future health. In the present review, we discuss the current literature regarding the association between systemic diseases and fertility, which may impact clinical outcomes or semen parameters. A number of conditions that have systemic consequences were identified, including genetic (e.g., cystic fibrosis, DNA mismatch repair alterations), obesity, psychological stress, exogenous testosterone, and a variety of common medications. As such, the infertility evaluation may offer an opportunity for health counseling beyond the discussion of reproductive goals. Moreover, male infertility has been suggested as a marker of future health, given that poor semen parameters and a diagnosis of male infertility are associated with an increased risk of hypogonadism, cardiometabolic disease, cancer, and even mortality. Therefore, male fertility requires multidisciplinary expertise for evaluation, treatment, and counseling. (Fertil Steril® 2020;■:■–■. ©2020 by American Society for Reproductive Medicine.)

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Infertility affects approximately 15% of all couples who are unable to successfully conceive after 1 year of trying (1, 2). Of the couples who are referred for evaluation, male factor infertility accounts for about 30% to 50%, with about 7% of all men worldwide labeled infertile at some point (3). As such, male infertility is both a men's health and a public health issue.

As sperm counts decline, presentations to both urologists and general practitioners offices will become more common (4). In addition, there is a growing body of evidence that male infertility may be a potential biomarker for later health. A man referred for evaluation after an abnormal semen analysis may thus benefit not only from fertility counseling but also from an assessment of general lifestyle factors, chronic disease management, and potential preventative health measures. In addition to optimizing a patient's reproductive outcomes, the clinician has an opportunity to both improve current health and prevent later morbidity and mortality associated with male infertility. The urologist's role in men's health is therefore evolving, as is the interdisciplinary management of their patients' general health. The purpose of the present review is to synthesize the existing data regarding the association between male fertility and overall health (both current and future).

SYSTEMIC INFLUENCES ON MALE INFERTILITY

Genetics

As up to 10% of the male genome is involved in reproduction and there are only 25,000 genes in the human genome, it is reasonable to assume that many genes also play a role in multiple organ systems and cell types. Indeed, many underlying genetic abnormalities that lead to clinical syndromes may have a negative impact on male fertility (5). For instance, DNA mismatch repair (MMR), which is known to be involved in spermatogenesis, plays an important role in maintaining the integrity of sperm DNA, as has been previously demonstrated in animal models, particularly with

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MLH1 (6). Defects in these repair mechanisms appear to translate to measurable effects in humans. Terribas et al. (7) found that in 13 patients with nonobstructive azoospermia or severe oligozoospermia all had significant reduction in expression of MMR-associated genes (e.g., *MLH1, MLH3, PMS2, MSH4,* and *MSH5*) compared with controls who had normal spermatogenesis; the degree in reduction of expression correlated with the severity of maturation arrest. Three single-nucleotide polymorphisms (SNPs) within *MSH1* and *MLH1* have been found to be associated with azoospermia and severe oligozoospermia as compared with healthy controls. Similarly, a case-control study of 1,292 men with idiopathic infertility found SNPs within *MLH1, PMS2,* and *MSH5* to be associated with either azoospermia or severe oligozoospermia. Clinically, mutations within MMR genes have been identified within Lynch syndrome patients though an effect on fertility was only noted in women (8). As such, these findings have yet to be incorporated into the routine evaluation of the infertile male.

Congenital bilateral absence of the vas deferens (CBAVD) is a well-known though uncommon cause of obstructive azoospermia. This congenital anomaly has long been associated with cystic fibrosis (CF) and is a key reason why the American Urological Association's best practice statement, "The Evaluation of the Azoospermic Male," recommends genetic testing for mutations within the CF transmembrane conductance regulator (*CFTR*) gene in select cases (9). Mutations within the gene have been confirmed within animal models such as mice to lead to obstructive azoospermia (10). In addition to known *CFTR* mutations, a number of previously unknown *CFTR* mutations have been found within obstructive azoospermic men when whole exon sequencing has been performed (11, 12). It is interesting that several *CFTR* mutations have also been identified in men without CBAVD and even in men with oligozoospermia/nonobstructive azoospermia, highlighting the importance of this gene in male reproduction (13). Knowledge of the association between CBAVD and CF can help guide couples toward genetic counseling for informed decision making. Conversely, clinicians caring for individuals with CF should have an understanding of the reproductive sequelae of the disease when caring for patients of reproductive age with CF.

Y-chromosome microdeletions are a known genetic cause of azoospermia and severe oligozoospermia (14). Moreover, identification of specific regional alterations (e.g., AZFa, AZFb, or AZFc) can help guide clinical management. A study of 4,000 Portuguese infertile men found that Yq microdeletions were present in 4.6% of patients, with the majority of these deletions associated with azoospermia rather than oligozoospermia (15). Also AZFc was found to be the most frequent microdeletion in 56.8% of cases, followed by AZFa (4.7%) and AZFb (4.0%). However, other studies have found the rate of Yq microdeletions in infertile males to be as high as 16.9% though with similar rates of AZFc mutations (53.6%) (16). These deletions do have an important clinical implication because men with AZFc mutations may be treatable with testicular sperm extraction whereas men with AZFa or AZFb mutations may be counseled about the reported futility of sperm extraction (17). Infertile men with AZFc mutations have rates of sperm retrieval, clinical pregnancy, and live birth of approximately 53%, 37.5%, and 25%, respectively (18).

Microdeletions are only present in men with low sperm concentrations; a study by Johnson et al. (19) of over 1,400 infertile men suggested that a threshold for genetic testing be 0.5 million/mL. Similarly, a systematic review by Kohn et al. (20) suggested that complete Yq microdeletions are rare in men who have a sperm concentration of more than 1 million/mL, so they suggested screening should be limited to those with oligozoospermia of <1 million/mL.

Testing for Y-chromosome microdeletion has a defined place within the fertility evaluation of the severe oligospermic or azoospermic male; however, recent data suggest they may have other health implications beyond reproduction. Systemically, Yq microdeletions may also affect overall health; these genes are also expressed in the brain, stomach, and urinary tract (21). Copy number variations (CNV) within AZFb and AZFc mutations were found to be associated with development of neuropsychiatric disorders (e.g., bipolar disorder, major depressive disorder, or language impairment) within a Chilean patient population of 42 men (22). An analysis of the UK Decipher database, which collects information on individuals with CNV, suggested similar findings: 71 men were found to have CNV within AZF genes, and 21 had either intellectual disorders or delayed development (21). Y microdeletions have also been associated with aberrations in pseudoautosomal regions (PARs) causing *SHOX* deficiency (23).

Klinefelter syndrome (KS), the most common chromosomal abnormality in males, has well defined systemic consequences (24). The majority of individuals with KS have a karyotype of 47,XXY (85%), mosaicism does exist with a range of X-chromosome copy numbers; of these individuals, 11% to 15% are estimated to be azoospermic (24, 25). Because these patients typically have primary testicular failure, they may present with hypergonadotrophic hypogonadism. As such, many will require surgical sperm extraction and assisted reproduction (e.g., in vitro fertilization, in vitro fertilization); however, fertility practices vary widely, particularly among adolescents, according to survey data (26).

Importantly, the systemic implications of KS—such as increased risks of insulin resistance, diabetes, dyslipidemia, cardiovascular disease, and thromboembolism—emphasize the relevance of the diagnosis extending beyond treatment for reproduction (24, 27, 28). It is interesting that a cohort study of more than 1,000 men with KS found the overall risk of solid tumors appeared to be decreased but the risk of hematologic malignancy was increased (29). However, despite this overall reduced risk of solid tumor, KS patients do have an increased incidence of breast cancer. Other urologic concerns for KS include sexual dysfunction and hypogonadism, often with the need for testosterone supplementation (30, 31). Given the systemic manifestations of KS, these patients may require specialty multidisciplinary care in addition to urologic consultation.

Infections

Infectious causes of male infertility range from isolated testicular causes to systemic infections with collateral impact on testicular function. Because the infection may be more proximal in the genitourinary tract (e.g., in the prostate) and may not have testicular symptoms, diagnosis of these as the underlying cause of infertility may be complex (32). The mechanisms of injury include direct insult within the infected tissue, inflammation, vasculitis, and endocrine disruption. Sexually transmitted infections of the genitourinary tract do not always cause symptoms, but they are a known cause of male infertility; the World Health Organization has recognized their important role and recommends considering work up if an infection is suspected (33). Inflammation, particularly in chronic or otherwise asymptomatic sexually transmitted infections, may lead to either impaired spermatogenesis or obstruction within the seminal tract.

Human papilloma virus (HPV) is the most common sexually transmitted virus in both men and women, and it has been associated with male fertility. Indeed, with the prevalence of HPV DNA in the semen of infertile men has been estimated to be up to 16%, and the virus has been implicated as an underlying cause of infertility in infected men (34). Moghimi et al. (35) found that in 70 infertile men, the 11.4% who had HPV DNA detected in their semen also had statistically significantly lower motility (23.5% vs. 32.2%) and morphology (7.13% vs. 15.18%), suggesting the negative impact of the virus. Furthermore, Boeri et al. (36) found that 15.5% of 729 infertile men had HPV in their semen, which was associated with lower progressive motility and higher DNA fragmentation index especially in the setting of high-risk HPV. In addition, a study of a cohort of 732 couples undergoing intrauterine insemination (1,753 cycles) demonstrated that the women inseminated with sperm that was HPV positive had four times fewer clinical pregnancies than those inseminated with HPV-negative sperm (37).

Chlamydia trachomatis, another common sexually transmitted infection, is asymptomatic in up to 50% of men (38). Although it has a well-known association with female infertility, less is known about its impact on male reproduction. It is interesting that *Chlamydia* antibodies were found in the serum of 72.2% of infertile men presenting to an Australian fertility clinic, with *Chlamydia* DNA detected in 16.7% of fresh testicular biopsy samples, although the clinical implications were unclear (38).

Human immunodeficiency virus (HIV) has been implicated in a number of genitourinary pathologies, and its presence has been documented in semen; however, there are few studies regarding a direct impact on fertility or semen parameters. HIV leading to acquired immunodeficiency syndrome (AIDS) is a known cause of testicular dysfunction and hypogonadism due to direct testicular damage (e.g., fibrosis, maturation arrest), but studies examining its role in fertility are lacking (39). Though the importance of the direct impact of AIDS on male fertility may be diminishing as HIV-positive status becomes a non-life-threatening chronic disease, the impact its treatment certainly becomes paramount. Pilatz et al. (40) found that among HIV-positive men on antiretroviral therapy, 25% had semen parameters less than the fifth percentile of the 2010 World Health Organization criteria.

Before widespread vaccination became available, mumps orchitis was a historical cause of male infertility, predominantly stemming from early childhood infection. Sertoli cells are one of the targets of the mumps virus (41). Wu et al. (41) demonstrated in a mouse model that mumps infection leads to disruption of the blood–testes barrier via impairment of various junctional proteins via TLR2-mediated tumor necrosis factor-α production, subsequently leading to reduced spermatogenesis. Moretti et al. (42) found that elevated serum levels of antibodies associated with chronic infections (e.g., *Helicobacter pylori, Mycoplasma pneumoniae, Chlamydophila pneumoniae,* Epstein-Barr virus, herpes simplex-1, and cytomegalovirus) were associated with a lower sperm concentration, sperm motility, and fertility index, especially if there were more than one antibody present. However, as comorbidities, clinical assessment, or global markers of inflammation were not assessed, it is difficult to establish a causal relationship between infection and semen quality. Pilatz et al. (43) found that a history of genitourinary infections was present in up to 27% of patients with azoospermia, but an infection did not seem to impact the rate of surgical retrieval of sperm.

Obesity

Obesity has become a public health crisis and can have profound pathophysiologic effects, ranging from diabetes to nonalcoholic fatty liver disease to coronary artery disease (44). It is thus reasonable to hypothesize that it may negatively impact spermatogenesis as well. Indeed, this has been demonstrated in several systematic reviews. Guo et al. (45) pooled data from 12 different studies on the effect of body mass index (BMI) or weight on semen parameters. They found a negative association between BMI and total sperm count, sperm concentration, and volume but not motility. For every 5 unit increase in BMI there was a 2.4% decrease in sperm count and a 2.0% decline in seminal volume. Before this, Sermondade et al. (46) examined 21 studies comprising 13,077 men and found that obesity was associated with oligozoospermia or azoospermia with odds ratios of 1.28 (95% confidence interval [CI], 1.06–1.55) and 2.04 (95% CI, 1.59–2.62), respectively. MacDonald et al. (47) pooled the results from 13 studies with a total of 6,793 men and found no association between BMI and semen parameters, but men are generally counseled on the negative association between obesity and male fertility.

Psychological Stress

Psychological stress, particularly when chronic, can lead to systemic effects causing disruptions in the immune system, vasculature, nervous system, and of particular importance for fertility, the hypothalamic-pituitary-gonadal (HPG) axis (48). Disruption within the HPG axis can lead to alterations in growth hormone levels, decreased prolactin, and reduced testosterone. As such, extrapolating the impact of psychological stress on spermatogenesis is not difficult, although most

studies have focused on the hormonal impact (e.g., alterations in gonadotropic and nongonadotropic hormones).

To look at the direct impact of psychological stress, Zou et al. (49) examined 384 men who were surveyed with a validated job content questionnaire to assess for work stress and also provided a semen sample. Those individuals that had higher work stress, as defined by the results of their job survey, had a higher risk of having a low sperm concentration (odds ratio 2.14; 95% CI, 1.24–3.68). It is interesting that if an individual with high stress also rated themselves as having high social support, the association was attenuated. Eskiocak et al. (50) examined a similar effect of school stress on semen quality in 29 healthy medical students just before and 3 months after their final examinations. During the period of stress before examinations, they noted a statistically significant drop in sperm concentration (41.28 $\pm$ 3.7 vs. 77.62 $\pm$ 7.13 $\times$ 10^6/mL) and progressive motility (8.79% $\pm$ 1.66% vs. 20.86% $\pm$ 1.63%), which recovered by 3 months after the examinations.

Finally, Bhongade et al. (51) used the Hospital Anxiety and Depression Score (HADS) to examine psychological stress and semen parameters in 70 male partners within infertile couples. A total of 27% of the men were categorized as having an abnormal (e.g., high) HADS. A higher HADS was associated with lower motility (40% vs. 60%), morphology (40% vs. 80%), and lower sperm count (25 vs. 63 million). Additionally, the investigators noted lower levels of testosterone and higher levels of gonadotropins (i.e., follicle-stimulating hormone and luteinizing hormone) in the men with higher HADS. Similarly, a study of 1,215 Danish men found that poor semen quality (e.g., volume, concentration, and total sperm count) were associated with higher levels of stress within a group administered the Copenhagen Psychosocial Questionnaire (52). It is interesting that there were no statistically significant differences in the levels of reproductive hormones across all stress levels. Psychological stress appears to have a potentially substantial impact on male fertility as well as its other negative systemic effects.

Medications and Substances

Aside from the direct cytotoxic effect of chemotherapeutics, the impact of medications on male fertility is not well known (53–55). As many reproductive-aged men take medications, it is important for clinicians to be aware of the potential effects that these medications may have on men's health. Many of the medications that are hypothesized to impact endocrine function may lead to disruption in the HPG axis, with a potential impact on testosterone levels and ultimately spermatogenesis.

A review by Semet et al. (56) established that many medications have a low level of evidence regarding their impact on male fertility. Exogenous testosterone has a well-documented negative impact on male fertility. Thus, 5α-reductase inhibitors have been hypothesized to negatively affect spermatogenesis through alterations in testosterone levels. A double-blind, placebo-controlled trial with 181 men found that treatment with 1 mg of finasteride did not affect total sperm, motility, or morphology but did decrease volume (−11%) (57). It is interesting that a similarly structured double-blind, placebo-controlled trial with 99 men found that treatment with 5 mg of finasteride or 0.5 mg of dutasteride was associated with statistically significantly decreased total sperm count (dutasteride −28.6% and finasteride −34.3%) at 24–28 weeks of follow up observation (58). After 52 weeks however, this reduction was not statistically significant compared with baseline. Additionally, at the 26-week follow-up evaluation, the finasteride group was noted to have statistically significant reductions in semen volume (−21.1%) and sperm concentration (−21.5%). The observed reductions in semen parameters reversed after cessation of treatment.

Two case reports also found men with infertility attributed to finasteride can have improvement in their semen parameters after cessation (59, 60). Furthermore, an evaluation of 4,400 men presenting for fertility evaluation found 27 that were taking finasteride (61). After discontinuation of finasteride there was a 11.6-fold increase in sperm counts though no effect was found on motility or morphology. Clinicians starting men on finasteride should consider counseling them on the potential negative effect it may have on spermatogenesis.

There are many underlying causes of hypogonadism leading to infertility, such as KS, hyperprolactinemia, hyperestrogenemia, and Kallmann syndrome (62). However, the treatment of hypogonadism may also impair fertility. This fact is especially important given data that suggest that up to 25% of urologists offer exogenous testosterone as a treatment for male infertility (63). Exogenous testosterone inhibits spermatogenesis. Indeed, Anderson and Wu (64) found that 18 months of once weekly testosterone supplementation led to either azoospermia or severe oligozoospermia. These findings echo those of Gaw Gonzalo et al. (65) who found that testosterone supplementation via patch or injection could lead to azoospermia or severe oligozoospermia.

Moreover, the number of men presenting to fertility clinics for evaluation who are found to be taking exogenous testosterone appears to be increasing (66). The return of spermatogenesis is not always guaranteed for men on previous therapy. A cohort study of 66 men with prior testosterone therapy examined their recovery rate (defined as total motile count >5 million sperm) at 12 months after cessation of the testosterone therapy and treatment with human chorionic gonadotropin or selective estrogen receptor modulators (67). Overall, 70% of men may recover spermatogenesis after cessation of testosterone therapy, but the chance of recovery decreases with longer duration of testosterone supplementation and older patient age. In addition, azoospermic men were found to have a rate of recovery of 64.8% versus 91.7% for cryptozoospermic men.

Blockage of the α_1-adrenergic receptor has been postulated as a method of male contraception by inducing retrograde ejaculation (although it is not effective for this purpose) (68). Indeed, in men taking tamsulosin, up to 90% have a decrease in ejaculatory volume, and 35% have anejaculation (69). Alfuzosin, on the other hand, appears not to cause anejaculation, possibility due to its selected α_1-adrenergic activity. In addition, tamsulosin was noted to have a

negative effect on motile sperm (−13.8%) (70). Any man who is started on an α-blocker should be appropriately counseled regarding its sexual side effects and associated fertility implications. The reverse (i.e., treatment α_1-adrenergic receptor agonist) has been shown to improve seminal parameters in select patients with ejaculatory dysfunction (71).

Several studies, though limited, have suggested a negative impact of various antidepressants on semen parameters. A case series of two individuals with oligospermia who were taking selective serotonin reuptake inhibitors (SSRIs) reported that after cessation of the medications there were substantial improvements in sperm concentration and motility (72). Tanrikut et al. (73) found a higher level of sperm DNA fragmentation (30.3%) compared with baseline (13.8%) in 35 men taking paroxetine for 5 weeks. In addition, compared with healthy men, 74 men taking SSRIs had decreased sperm motility (48.2% ± 4.6% vs. 66.2% ± 4.4%) and total sperm count (61.2 ± 11.4 vs. 186.2 ± 31.4 million) (74). Although the level of evidence is low, it appears that antidepressants may have a negative impact upon male fertility.

With the increasing legalization of marijuana in the United States, there has been more attention directed toward its potential associations with male reproduction. In a study by Nassan et al. (75), no differences in semen quality were noted among 662 subfertile men presenting to a fertility center based on marijuana use. Additionally, in couples using assisted reproductive technologies to conceive, male partners who currently smoked marijuana had cycles with a higher probability of live birth compared with former smokers or nonsmokers (76). By contrast, two studies (n = 229 and n = 1,215) found that regular marijuana use was associated with lower sperm motility, total sperm count, and sperm concentration (77, 78). These findings were echoed by a recent systematic review of marijuana use that combined clinical and preclinical data and concluded a negative association between marijuana use and male fertility. However male fertility was identified based on semen parameters, gonadotropin levels, or testosterone levels and not clinical outcomes such as pregnancy (79). In an analysis of the National Survey of Family Growth, marijuana use was not associated with time to pregnancy in men or women (80). Thus, the data on marijuana use and male fertility remains heterogenous.

Although many effects of the opioid crisis have been described, less attention has been focused on its association with male fertility (81). Opioids are known to disrupt the HPG axis through inhibition of gonadotropin-releasing hormone, which disrupts the reproductive system (82). Farag et al. (83) found that individuals who abused tramadol (an opioid analgesic) compared with nonusers had statistically significantly lower progressive motility (39.5% ± 18.2% vs. 75.2% ± 5.9%) and concentration (44.7 ± 24.8 vs. 51.3 ± 22.6 million/mL). Additionally, they found a negative impact on testosterone levels (2.0 ± 0.9 vs. 5.8 ± 2.0 ng/mL) with associated elevated gonadotropins. Not only is the HPG axis disrupted in opioid use, Chorbov et al. (84) also found that DNA methylation patterns were altered in the sperm of chronic opioid users compared with nonusers. Similarly, Safarinejad et al. (85) found decreased sperm concentration in chronic users versus nonusers (22.2 ± 4.4 vs. 66.3 ± 8.3 million/mL). They also noted higher levels of DNA fragmentation among the chronic users. Chronic opioids, through a variety of potential mechanisms, appear to have a negative impact upon male reproduction.

MALE INFERTILITY AND FUTURE HEALTH

The underlying link for infertility as a potential marker of future health is unknown. Several factors have been hypothesized to play a role in this association, such as developmental, hormonal, lifestyle, genetic, or epigenetic factors (86). As previously mentioned, a large portion of the genome is involved with fertility, so the genes involved in reproduction may also be expressed in other cell types. In addition, epigenetic alterations may lead to global changes in expression, thus affecting spermatogenesis as well as other body functions.

Cancer Risk

Several studies have suggested that male infertility is associated with an increased risk of cancer, thus acting as a potential biomarker (87, 88). The relationship between infertility and testicular cancer has been well studied. Several studies in different countries have demonstrated a higher risk of testis cancer among infertile men (87, 89–93). Moreover, among men evaluated for infertility, those with lower semen quality had a higher risk of testis cancer.

The association between male infertility and incident prostate cancer has also been examined. Walsh et al. (94) found that men with male factor infertility were at higher risk for the development of high-grade prostate cancer. A Swedish study also demonstrated that infertile men conceiving with in vitro fertilization (IVF) or IVF with intracytoplasmic sperm injection had a high of prostate cancer compared with men who conceived without assistance (95). However, other studies have not demonstrated a higher risk of prostate cancer (87, 91).

Among infertile men, one study suggested that azoospermic men may be at highest risk of cancer (96). In addition, the risk of cancer does not appear to be limited to the infertile male: several studies have suggested that there may be a familial risk among men with either male factor infertility or poor semen parameters (88, 97, 98). Although the data on testis cancer is well established, further research is needed to determine whether the risk of other malignancies is higher among infertile men and their relatives.

Cardiovascular Disease, Hypertension, and Diabetes

Male infertility as a potential marker of incident cardiometabolic disease is increasingly important given the prevalence of chronic illness and cardiovascular deaths in the United States. Identifying a causal link may be particularly useful during the work up of infertile men: a diagnosis of infertility could trigger preventive medicine measures. Several cohort studies found that an infertility diagnosis was associated with an increased risk of comorbidity including hypertension (99–101). Eisenberg et al. (99) found that men diagnosed with

male factor infertility had an increased risk of incident cardiovascular disease. Kasman et al. (102) demonstrated that this risk spans sociodemographic strata. Additionally, Latif et al. (103) found that men with a sperm concentration <15 million/mL had a higher risk of cardiovascular disease (hazard ratio 1.4; 95% CI, 1.2–1.6). Male fertility may additionally be a marker for future diabetes risk. A U.S. study demonstrated that infertile men are at a higher risk of incident diabetes in the years after an infertility diagnosis (hazard ratio 1.81; 95% CI, 1.57–2.08) (99). Two other large studies with more than 39,000 men within infertile couples and 744 infertile men found similar findings risk of diabetes development (104, 105). It is interesting that Boeri et al. (104) noted that up to 15% of infertile men may have undiagnosed diabetes or prediabetes.

Mortality

Male infertility has also been associated with premature mortality. Certain comorbidities and habits associated with male infertility—such as smoking, obesity, and alcohol consumption—are also risk factors for early mortality and thus act as potential confounders in studies, but there may be an independent association (106). Among over 43,000 men referred for a fertility evaluation, Jensen et al. (107) reported an inverse relationship between semen quality and mortality among both fathers and childless men. Glazer et al. (108) reported that men with male factor infertility had an increased risk of death among infertile compared with fertile men (hazard ratio 1.27; 95% CI, 1.12–1.44) with the highest risk among men with azoospermia. A U.S. study of 11,000 infertile men found that men with lower semen quality had a higher risk of death (109). Finally, a cohort study of more than 43,000 Swedish men found that those diagnosed with infertility had a higher risk of death before age 30 (adjusted hazard ratio 3.24; 95% CI, 2.42–4.41) mostly due to a higher risk of early cancer (110). However, overall there was no increased risk of death related to infertility (adjusted hazard ratio 0.98; 95% CI, 0.89–1.08).

Hypogonadism

Testosterone is important for male reproductive health, so alterations in its levels may lead to impairment of spermatogenesis. Additionally, testosterone deficiency can impair health in several ways such as elevated BMI, hypertension, dyslipidemia, elevated HbA1c, and decreased bone mineral density (111–114). Importantly, reversal of hypogonadal status may lead to improvements in depression, quality of life, libido, and bone mineral density (111–114). As such, detection of hypogonadism is important, and identification of male infertility could trigger testosterone testing and follow-up endocrine evaluation.

A number of studies have identified an increased risk of hypogonadism (defined by laboratory values, not necessarily associated with symptoms) in infertile populations as compared with healthy controls (115–118). Jørgensen et al. (119) evaluated the potential impact of various semen parameters on testosterone levels in more than 8,000 healthy young men but did not find an association between testosterone and lower semen quality. However, this study was done in healthy men, so screening for hypogonadism may be most beneficial for infertile men. Nevertheless, poor semen parameters should trigger clinicians to evaluate for endocrinopathy (e.g., hypogonadism) and associated comorbidities (120, 121).

Autoimmune Conditions

Investigators have sought to find other associations of medical conditions with male fertility status as a potential biomarker. In a cohort of over 24,000 Danish men, Glazer et al. (122) found that men with male factor infertility had higher odds of having multiple sclerosis (odds ratio 1.61; 95% CI, 1.04–2.51). Using a U.S. cohort, Brubaker et al. (123) found that infertile men had a higher risk of autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, psoriasis, Grave's disease, multiple sclerosis).

CONCLUSION

The evaluation of infertile men should not only focus on the singular goal of pregnancy but also provide a comprehensive and potentially multidisciplinary evaluation to help improve reproductive and overall health. Given the complex nature of reproduction, overall health plays an integral role to successful spermatogenesis. Alterations to health can negatively impact a man's fertility status. Thus, a diagnosis of male infertility may serve as a potential biomarker for current and future health.

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