



Comprehensive men's health and male infertility

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Abstract: There is increasing evidence that male infertility may be a harbinger of comorbid medical illness. Existing studies have shed light on associations between infertility and the prevalence of cardiovascular, metabolic, and oncologic disease, along with rates of hospitalization and overall mortality. Although theorized mechanisms include genetic, developmental, and behavioral precipitants, the exact nature of these associations remains unclear and warrants further investigation.

Keywords: Male infertility; men's health; spermatogenesis; mortality

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Introduction

Infertility, or the inability to conceive after one year of unprotected intercourse, is thought to affect approximately 15% of couples worldwide (1). Twenty percent of these cases are due to male infertility alone, while 30% arise from a combination of male and female infertility factors (2,3). Recent studies have begun to shed light on associations between male infertility and other medical comorbidities, although the exact mechanisms behind these associations remain elusive. The goal of this article is to review the existing literature supporting these associations and to consider various hypothesized factors which may be driving them.

Male infertility and comorbid medical disease

A recent large scale study comparing 3,328 infertile men in Japan with 452 fertile male controls showed that the prevalence of medical comorbidities was significantly higher in the infertile men (21.7% versus 9.1% respectively), and further demonstrated that treatment of medical comorbidities effected a significant improvement in total motile sperm count over baseline and over men with

untreated comorbidities (4). Concerning the comorbidities involved, the study found the highest prevalences were hypertension (17.8%) and hyperlipidemia (5.9%). An alternate cross-sectional study of over 9,000 men noted increasing comorbidity indices seen with decreases in sperm concentration, motility, and seminal volume, with comorbid hypertension, cardiac disease, and peripheral vascular disease being chiefly associated with these seminal parameter impairments (5). Indeed, there has been much prior work that points to associations between male infertility and both cardiovascular disease and metabolic disease. Hypertensive men have been found to have lower testosterone levels compared to their normotensive counterparts (6,7), and one study in particular demonstrated lower semen volume, sperm count, and sperm motility in hypertensive patients (8). There are additional studies focusing on cardiovascular disease which have used imperfect surrogate variables for infertility; for example, a 2011 investigation utilizing data from the NIH-AARP Diet and Health Study demonstrated that men who had not fathered children had an increased risk of cardiovascular mortality during the approximately decade-long study period, although notably in this scenario, childlessness did not necessarily connote infertility (9). Another more recent study showed that men diagnosed with

infertility had a higher likelihood of developing ischemic cardiac disease compared to fertile men (10).

Other studies have assessed the link between male infertility and metabolic disease. Epidemiologists have reported a worldwide deterioration of semen quality over the past 50 years (11), which has coincided with the growing obesity pandemic. Obesity itself has been associated with increased rates of oligospermia and azoospermia with a J-shaped association noted between body mass index (BMI) and risk of sperm concentration impairment (12), while hypercholesterolemia has been associated with impairments in sperm morphology (13). Men diagnosed with infertility have been found to be at an increased risk of developing diabetes mellitus (10), and conversely, an increased risk of infertility has been found amongst diabetic men (14).

There also exists an impressive body of literature connecting male infertility with oncologic disease. Multiple studies have reported a link between infertility and testicular cancer. One large scale study of 32,000 men over 30 years in Denmark detected an association between impaired sperm concentration, motility, and morphology with testicular cancer (15), while another study of 51,000 infertile couples in the US demonstrated a threefold increased risk of testicular cancer associated with male infertility (16). Oncologic risk does not seem to be limited to testicular cancer, as a 2013 American study which used insurance claims to identify a group of 76,000 infertile men also found elevated rates of all cancer types, and specifically non-Hodgkin's lymphoma, in the infertile men as compared to controls (17). The data surrounding infertility and prostate cancer is far more muddled, with conflicting studies having previously reported increased risk, decreased risk, and no detectable association between prostate cancer and male infertility (18-20).

Male infertility and mortality

Male infertility has also been implicated as a harbinger of hospitalization. A study out of Denmark looking at 4,712 men who had presented for infertility workup concluded that impairments in sperm concentration and motility correlated with increased hospitalization rates (21). Furthermore, as the scope of investigation has expanded to assess a potential relationship between infertility and mortality, a Danish study of the semen analyses of 43,000 infertile men found mortality to decrease as sperm motility, morphology, and concentration increased, with up to a

limit of 40 million sperm per milliliter in the case of the latter parameter (22). Meanwhile, an American study of 11,935 infertile men showed that decreased sperm motility, concentration, and seminal volume correlated with increased mortality rates, and also that men with at least two deficiencies in seminal parameters had a 2.3-fold higher mortality risk (23).

Potential associative etiologies

While the exact mechanisms governing the relationship between male infertility and medical comorbidity remain unclear, multiple hypotheses have arisen to account for the apparent associations. The first is a genetic etiology, with a fertility impairing mutation having a potential downstream effect giving rise to other disease processes. Multiple examples of this phenomenon have already been noted, including CFTR mutations which result in cystic fibrosis along with the fertility-impairing congenital bilateral absence of the vas deferens (24), MLH1 mutations which cause both Lynch syndrome and nonobstructive azoospermia (25), and ERCC1 and MSH2 mutations which can give rise to colorectal cancer in addition to nonobstructive azoospermia (26-29). Most notably, Klinefelter syndrome, resulting from aneuploidy of sex chromosomes, is known to effect primary hypogonadism, while also conferring an increased risk of cardiovascular disease, diabetes mellitus, and various cancers (30-32). Additionally, Y chromosomal microdeletions can cause severe fertility impairment, and in some cases, contribute to short stature by way of involvement of the *SHOX* gene (33). In addition to isolated gene mutations, emerging data also suggests that aberrant epigenetic changes may give rise to sperm abnormalities and infertility, as studies have identified altered epigenetic profiles in the sperm of oligospermic men (34).

An alternative associative theory is based upon the theorized testicular dysgenesis syndrome, which links seminal parameter impairment with other genitourinary pathologies including cryptorchidism, hypospadias, and testicular cancer, and suggests that an inciting event during embryogenesis could be responsible for disrupted gonadal development and may promote the development of other disease processes later in life (35). Implicated precipitants may include environmental factors and assisted reproductive technologies (36). Indeed, certain studies have shown that IVF/ICSI (*in vitro* fertilization/intracytoplasmic sperm injection)-conceived babies tend

to have higher rates of hypospadias, cryptorchidism, and preterm birth, the latter of which predisposes them to the development of cardiovascular disease and diabetes (37-39). ICSI-conceived males have also been found to have lower sperm concentrations and counts as compared to naturally conceived controls (40).

Finally, lifestyle or psychosocial variables have been suspected to play a role in the association between infertility and comorbidity. While the data linking infertility and obesity, itself a predisposing factor to other chronic illness, have been previously discussed, noxious behaviors such as tobacco and alcohol overuse can also have negative effects on both general health and fertility. Through a meta-analysis, smoking has been shown to contribute to impairments in sperm concentration, motility, morphology, and semen volume (41). The data surrounding alcohol abuse is more equivocal, however, with some studies noting alcohol-associated reduction in semen volume, while others have noted no adverse effects of moderate alcohol intake on seminal parameters or conception rates (42,43). Even psychological stress has been found to negatively impact sperm concentration, morphology, and motility (41).

Conclusions

The existing body of literature has highlighted an apparent relationship between male infertility and other systemic pathologies, including cardiovascular, metabolic, and oncologic disease. While genetic, developmental, and psychosocial catalysts have been recognized, there is still much investigative work to be done to further identify and elucidate the mechanistic drivers behind the association between infertility and medical comorbidity. As fertility impairment could potentially serve as a biomarker of health, providing clinicians with preventive insight into the development or progression of other chronic diseases, a better understanding of these associations would be paramount to promoting the optimal care of a man's overall health.

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