Male Infertility and Somatic Health

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KEYWORDS

• Male infertility • Men's health • Somatic health

KEY POINTS

- Somatic health is associated with male infertility.
- Potential links between male infertility and health include genetic, developmental, and lifestyle factors.
- Male infertility also may be a predictor of oncologic, cardiovascular, metabolic, autoimmune diseases, hospitalization and mortality.
- Additional research is required to elucidate the mechanisms by which male infertility affects overall health.

INTRODUCTION

Humankind has been interested in reproduction for millennia, as it is the primary instinct of all organisms and it is a social, cultural, and medical issue. Infertility and surrogacy are first mentioned on a 4000-year-old Assyrian clay tablet of a marriage contract exhibited at Istanbul Archeology Museum in Turkey.[1]

Infertility is defined as the inability to conceive after 1 year of unprotected intercourse.[2] Agarwal and colleagues[3] documented that the estimated number of couples with infertility worldwide is 48.5 million and calculated rates of male infertility across the globe.

Approximately 15% of couples are affected by infertility, with male factor infertility thought to play a role in 50% of infertile couples, acting as the sole contributor in 20% to 30% of infertility cases.[4,5] There exists a growing body of literature that would suggest an association between male infertility and a host of other medical conditions, including oncologic, cardiovascular, autoimmune, and other chronic diseases, to broader outcomes such as hospitalizations and mortality. The exact nature of these associations remains unclear, although popular hypothesized etiologic mechanisms include genetic, developmental, and lifestyle-based factors. The purpose of this review was to survey the existing data of these associations, to provide a better understanding of the relationship between male infertility and overall somatic health, in addition explore some of the new ideas in the field.

GENETIC ASSOCIATIONS

Given that approximately 10% of the human genome is involved in reproduction, it is reasonable to assume that a genetic mutation affecting

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reproduction could also affect another organ system. For example, Klinefelter syndrome (47, XXY genotype) is a genetic cause of primary hypogonadism, which leads to male infertility in addition to the extragonadal phenotypic manifestations of the syndrome, such as an increased risk of cardiovascular disease, metabolic syndrome, insulin resistance, diabetes mellitus, and cancer.[6–8] Another classic example is a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which can result in congenital bilateral absence of the vas deferens or epididymal obstruction leading to male infertility, while also giving rise to a cystic fibrosis phenotype.[9]

Next, mutations in the *MLH1* gene, which give rise to Lynch syndrome, also have been identified in men with nonobstructive azoospermia (NOA).[10] *ERCC1* and *MSH2* are other genes that have been found to be involved in DNA mismatch repair,[11,12] nonobstructive azoospermia, and the development of colorectal cancers.[13,14] In addition, there is evidence that men with NOA demonstrate higher rates of defects in DNA repair mechanisms and cell cycle regulation, and higher rates of cancer have been found in azoospermic men.[15,16] Next, men with NOA also have shorter telomere lengths, which have been associated with premature aging.

Deletions involving the Y chromosome can impair spermatogenesis.[17] Y chromosome microdeletions can also involve the *SHOX* (short-stature homeobox) gene, the haploinsufficiency of which can give rise to short stature.[18] It was found recently that there is a relationship of 4 potentially functional polymorphisms associated with oxidative stress pathway genes (superoxide dismutase-SOD2 Ile58Thr and SOD2 rs4880, catalase-CAT C-262T, glutathione peroxidase 1-GPX1 Pro200Leu) and increased male infertility risk.[19]

In addition, Ben Rhouma and colleagues[20] stated that 33 genes have been identified as responsible for nonsyndromic male infertility. The evolution of techniques based on whole-genome analysis has allowed the development of more successful methods in the identification of new genes and mutations inducing an infertility phenotype. As such, new genetic links between reproductive and somatic health are likely to arise.

DEVELOPMENTAL ASSOCIATIONS

Hypothesized by David Barker,[21] the concept of fetal origins of adult disease posits that intrauterine events can impact an individual's risk of developing diseases in adult life.[22] In a similar way, the testicular dysgenesis syndrome (TDS), introduced by Skakkebaek and collegues,[23] suggests in utero exposures can alter normal genital growth and development. TDS links several male genital anomalies, including poor semen quality, hypospadias, cryptorchidism, and testicular cancer. Although the causes are unclear, environmental exposures, including chemical exposures or assisted reproductive technologies, have been suggested.[24] Indeed, children conceived through in vitro fertilization and intracytoplasmic sperm injection have been found to have higher rates of cryptorchidism and hypospadias, as well as higher rates of preterm birth and low birth weight.[25] In addition, preterm infants are at higher risk for a variety of systemic diseases, including cardiovascular disease and diabetes.[26,27] Next, studies have demonstrated that young men conceived via intracytoplasmic sperm injection have lower sperm concentrations and total sperm counts compared with boys conceived without assistance[28] On the other hand, among men undergoing infertility evaluation, there is no significant relationship between semen parameters and defect rates in live or still births, even when considering mode of conception.[29]

LIFESTYLE ASSOCIATIONS

In a similar way that many lifestyle factors are associated with the development of chronic disease, studies suggest a relationship between lifestyle factors and male infertility. Current data suggest that obesity negatively impacts male fertility. A meta-analysis of 21 studies, including those performed by Sermondade and colleagues,[30] demonstrated that as body mass index (BMI) increased, so did the odds of oligospermia and azoospermia. BMI provides another link between fertility and chronic disease, as overweight and obese men are at risk for adverse health outcomes. Obesity was associated with lower semen volume, lower sperm motility, and erectile dysfunction in infertile couples.[31] However, there is sufficient literature to support that weight reduction by diet and exercise, smoking cessation, and alcohol moderation are positive in male fertility.

Certain lifestyle habits, such as tobacco use, have negative health and reproductive effects. A meta-analysis performed by Li and colleagues[32] showed that smoking is an independent risk factor for reduced semen quality. In contrast, the association between male fertility and alcohol consumption is uncertain, as studies have suggested that moderate alcohol intake is not adversely associated with semen quality.[33] Another study found no association with the probability of conception and alcohol consumption in men.[34]

Next, there is increasing evidence that current health is associated with male fertility. Salonia and colleagues[35] demonstrated that infertile men had a significantly higher rate of comorbidities (as measured by the Charlson Comorbidity Index [CCI]) in comparison with their fertile controls. A subsequent cross-sectional study of 9387 men showed that increasing CCIs were associated with decreased semen volume, sperm concentration, sperm total count, and sperm motility. When looking at specific comorbidities, men with hypertension, cardiac disease, and peripheral vascular disease were found to have increased rates of seminal parameter abnormalities.[27] In addition, there is evidence that treatment of medical comorbidities can improve fertility. Shiraishi and Matsuyama[36] found that men who were successfully treated for various medical comorbidities (eg, hypertension, hyperlipidemia) had significant improvements in their total motile sperm counts.

Infectious etiologies may also affect somatic and reproductive health. For example, schistosomiasis, which is endemic in some developing countries, may induce infertility, due to hormonal imbalance, testicular tissue damage, and genital ductal system obstruction.[37] Human papillomavirus (HPV) may be risk factor for male infertility, as some studies have shown a higher prevalence of high-risk HPV in infertile men than fertile men.[38]

MALE INFERTILITY AND ONCOLOGIC DISEASE

Cancer and its therapy can impair male fertility.[39] However, emerging evidence suggests a link between male infertility and risk of incident malignant disease. The best-studied example is the association between infertility and testicular cancer. Many groups have explored this relationship. A Danish cohort study examined more than 30,000 men and reported that low sperm concentration, decreased sperm motility, and poorer sperm morphology were each independently associated with an increased incidence of testicular cancer.[40] In addition, a large American multicenter cohort study of more than 51,000 infertile couples in California found that diagnosed male factor infertility was associated with a nearly threefold increase in the incidence of testicular cancer.[41] Another American study used commercial insurance claims data to examine more than 75,000 infertile men and found that the group of infertile men had higher rates of all cancers, testicular cancer, as well as non-Hodgkin lymphoma.[42] Although the etiology between male infertility and testicular cancer require more study, as discussed earlier, hypothesized potential mechanisms include developmental, genetic, and environmental etiologic factors.

A link between infertility and prostate cancer is uncertain, with conflicting data in the literature. A 2010 retrospective cohort study looking at 22,562 California men who had undergone fertility testing demonstrated that men with infertility were at an increased risk for developing high-grade prostate cancer but not overall prostate cancer.[43] Conversely, a 2016 retrospective cohort study of 20,433 men who underwent semen analysis found no association between infertility and prostate cancer risk.[44] In addition, a Swedish nested case-control study of 445 patients with prostate cancer reported lower odds of developing prostate cancer in infertile men.[45]

Interestingly, there are recent data suggesting that male infertility may serve not only as a biomarker for an individual man's health, but also as a marker of oncologic risk for the affected man's family members.[46] A 2016 study revealed that first-degree relatives of the men who underwent semen analysis had a 52% increased risk of testicular cancer, as compared with the first-degree relatives of the fertile controls. In addition, first-degree and second-degree relatives of men with azoospermia were found to have an increased risk of thyroid cancer.[47] Furthermore, a subsequent retrospective cohort study of 10,511 men from Utah who had undergone semen analysis and their 63,891 siblings and 327,753 cousins revealed that oligospermia was associated with a twofold increase in risk of childhood cancer in the subfertile man's siblings, as well as a threefold risk of specifically acute lymphoblastic leukemia in the siblings, as compared with the siblings of fertile controls.[48] Although the origins of these familial associations are unclear, shared genetics or environment provide plausible mechanisms.

MALE INFERTILITY AND NONONCOLOGIC CHRONIC DISEASES

An association also has been suggested between male infertility and cardiometabolic disease. Although prevalent cardiovascular disease is associated with impaired semen quality, as a recent study found hypertensive men to have lower seminal volume, sperm count, and sperm motility compared with men without the diagnosis of hypertension,[49] the question of incident cardiovascular disease after a male infertility diagnosis is uncertain. To date, many of the studies undertaken thus far have used surrogate markers for infertility, thus limiting the interpretability of the data. For example, one study assessed

fatherhood (ie, having children or not) and the risk of cardiovascular disease using data from the National Institutes of Health–AARP Diet and Health Study, and found that childless men had an increased risk of death from cardiovascular disease compared with fathers.[50] However, childlessness serves as an imperfect surrogate for infertility, given that childless men may not necessarily be infertile.

A study examining US insurance claims data demonstrated that men diagnosed with male factor infertility were at increased risk of developing ischemic heart disease relative to control groups.[51] In addition, a US study noted that men with varicoceles have a higher incidence of heart disease.[52] Although varicoceles may contribute to male infertility, the presence of a varicocele does not necessarily imply infertility.

Given that low semen quality is associated with obesity,[30] further work has suggested that lipid concentrations may negatively impact semen parameters, as higher serum levels of total cholesterol and phospholipids have been associated with poorer sperm morphology.[53] Other studies have identified an increased prevalence of infertility in men with type 2 diabetes mellitus,[54] as well as increased risk of incident diabetes among those diagnosed with male factor infertility.[51]

A Danish study of more than 24,000 infertile men demonstrated that infertile men had higher risk of both prevalent and incident multiple sclerosis.[55] Given the suspected autoimmune nature of the pathogenesis of multiple sclerosis, another study used insurance claims data to assess for a relationship between male infertility and autoimmune diseases, and found that a cohort of infertile men had a higher risk of developing incident rheumatoid arthritis, psoriasis, multiple sclerosis, Graves' disease, and autoimmune thyroiditis.[56] Although the mechanism of the proposed association between infertility and autoimmunity remains unclear, evidence suggests that androgens may modulate immunity.[57]

In addition, a Danish study of men evaluated for infertility found that decreased sperm concentration, total sperm count, and sperm motility were associated with increased rates of all-cause hospitalizations. Specifically, sperm concentrations less than 15 million/mL were clearly associated with an increased risk of being hospitalized.[58] As with earlier work, causation remains uncertain. Factors related to health or lifestyle that could simultaneously affect a man's fertility and health could explain the identified associations. However, Latif and colleagues[59] examined a large Danish cohort and reported no effect modification based on lifestyle, fertility status, health, and socioeconomic status, suggesting a biological explanation for the association between fertility and hospitalization.

MALE INFERTILITY AND MORTALITY

Given the link between male infertility and chronic disease, researchers have examined the association between infertility and mortality. An analysis of a historic German cohort of 600 men over the span of 35 years failed to establish a relationship between semen quality and mortality, although subgroup analysis suggested a possible association among older members of the cohort.[60] However, given that the study was limited to subjects who lived in post–World War II Germany, the generalizability of the results remains questionable. More recently, Jensen and colleagues[61] evaluated a cohort of more than 43,000 Danish men who had semen analyses performed in the setting of infertility, and found that mortality decreased as sperm concentration increased. Mortality was also found to decrease in a dose-response manner, as sperm motility, morphology, and semen volume increased. A subsequent multicentered American cohort study of more than 11,000 men demonstrated that men with impaired semen parameters (specifically decreased semen volume, sperm concentration, sperm motility, and total sperm count) had significantly higher mortality rates compared with men with normal semen parameters. Specifically, men with 2 or more abnormal semen parameters were found to have a 2.3-fold higher risk of death, although overall incidence of mortality in the study was less than 1%.[62]

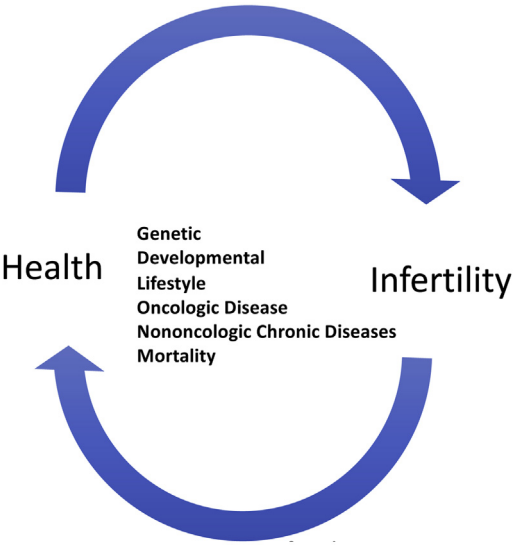

Fig. 1. The relationship between male infertility and overall somatic health.

SUMMARY

A review of the current data suggests that semen quality and male fertility may be a biomarker of overall health (**Fig. 1**). There is a growing body of evidence indicating that male infertility is associated with increased risk of prevalent and incident oncologic, cardiovascular, metabolic, and autoimmune disease, as has also been shown for women. Although the purported associations may arise from genetic, developmental, or lifestyle-based origins, the exact nature of these associations remains unclear. Additional research is required to determine the potential mechanisms and to further clarify the relationship between male infertility and overall health.

DISCLOSURE

The authors have nothing to disclose.

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