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Male infertility as a window to health

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There is an emerging body of evidence suggesting that male infertility may be a harbinger of future health. Potential associations between infertility and health may arise from genetic, developmental, and lifestyle factors. Studies have explored possible links between male infertility and oncologic, cardiovascular, metabolic, and autoimmune diseases. Male infertility may also be a predictor of hospitalization and mortality. Additional research is required to elucidate the mechanisms by which male infertility affects overall health. (Fertil Steril® 2018;110:810–4. ©2018 by American Society for Reproductive Medicine.)
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Infertility is defined as the inability to conceive after 1 year of unprotected intercourse (1). 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% of infertility cases and contributing jointly with a female infertility factor in ~30% of cases (2, 3). There exists a growing body of literature that suggests an association between male infertility and a host of other medical conditions, ranging from oncologic, cardiovascular, autoimmune, and other chronic diseases to quantifiable outcomes such as hospitalization rates and mortality. The exact nature of these associations remains somewhat unclear, although hypothesized mechanisms include genetic, developmental, and lifestyle-based factors. The purpose of the present review is to survey the existing data in support of these associations to provide a better understanding of the relationship between male infertility and overall health.

GENETIC ASSOCIATIONS

Considering that ~10% of the human genome is involved in reproduction, it stands to reason that a genetic mutation affecting male fertility could have a concurrent effect on other physiologic processes as well. Among several examples of this phenomenon are cystic fibrosis transmembrane conductance regulator gene mutations, which can result in congenital bilateral absence of the vas deferens leading to male infertility while also giving rise to a cystic fibrosis phenotype (4). In addition, mutations in the *MLH1* gene which give rise to Lynch syndrome have also been identified in men with nonobstructive azoospermia (NOA) (5). *ERCC1* and *MSH2* are other genes which, like *MLH1*, have been found to be involved in DNA mismatch repair, NOA, and the development of colorectal cancers (6–9). Although the exact etiology of NOA is unknown, 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 (10). Klinefelter syndrome (KS) is a well known genetic cause of primary hypogonadism, which arises from sex chromosomal aneuploidy, typically with a 47,XXY genotype, although mosaicisms are possible as well, and can give rise to male infertility in addition to the extragonadal phenotypic manifestations of the syndrome. Notably, patients with KS are found to have increased risks of cardiovascular disease, metabolic syndrome, insulin resistance, diabetes mellitus, and cancer, particularly male breast cancer, but potentially lung cancer and non-Hodgkin lymphoma as well (11–13). Finally, deletions involving the Y chromosome can severely impair fertility, with ~10% of azoospermic men harboring Y chromosome microdeletions, making genetic testing for Y microdeletions a routine part of diagnostic evaluation in this population of infertile men (14). Y chromosome microdeletions can also involve the *SHOX* (short-stature homeobox) gene, the haploinsufficiency of which can give rise to short stature (15).

DEVELOPMENTAL ASSOCIATIONS

Pioneered by David Barker, the concept of fetal origins of adult disease (FOAD) holds that owing to "developmental plasticity," intrauterine events can have a profound impact on an individual's risk of developing diseases later in adult life (16, 17). Functioning as a

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corollary to the FOAD hypothesis, the testicular dysgenesis syndrome introduced by Skakkebaek et al. unites a phenotypic constellation including poor semen quality, hypospadias, cryptorchidism, and testicular cancer and postulates that this constellation arises from a disruption of embryonal and gonadal development that occurs during fetal life (18). Although the exact culprits are unclear, environmental exposures are thought to play a role, and an increasing reliance on assisted reproductive technologies has been implicated as well (19). By this hypothesis, it would appear that developmental events can also be associated with incidence of future disease processes. Children conceived through in vitro fertilization and intracytoplasmic sperm injection (ICSI) have been found to have higher rates of cryptorchidism and hypospadias, as well as higher rates of preterm birth and low birth weight (20). Preterm babies are then found to be at higher risk for a variety of systemic diseases, including cardiovascular disease (21) and both type 1 and type 2 diabetes mellitus (22). In addition, studies of semen quality in young men conceived via ICSI have demonstrated lower median sperm concentrations and total sperm counts compared with their spontaneously conceived peers (23).

LIFESTYLE ASSOCIATIONS

As various lifestyle factors have been implicated in the development of many chronic diseases, there similarly exists an association between lifestyle factors and male infertility. The existing data are strongly suggestive of an inverse relationship between body mass index (BMI) and fertility, with a large meta-analysis of 21 studies including 13,077 men performed by Sermondade et al. confirming a "J-shaped" relationship between BMI and risk of oligospermia and azoospermia (24). With overweight and obese men already at risk for adverse health outcomes, BMI provides another link between fertility and chronic disease. Toxic lifestyle habits such as tobacco and alcohol abuse have well established deleterious health effects, and a meta-analysis performed by Li et al. showed that smoking is an independent risk factor for reduced semen volume, sperm concentration, sperm count, sperm motility, and sperm morphology, and alcohol was found to reduce semen volume. Interestingly, in the same study, psychologic stress was also found to be associated with decreased sperm concentration, motility, and morphology (25). The relationship between fertility and alcohol is less clear, however, because other studies have suggested that moderate alcohol intake is not adversely associated with semen quality (26). Another study demonstrated decreasing probability of conception with increasing alcohol consumption in women, although no such dose-response relationship was seen in the men involved in the study (27). There is increasing evidence that current health status bears an association with fertility as well. A prospective case-control study undertaken by Salonia et al. demonstrated that infertile men had a significantly higher rate of comorbidities compared with fertile control men (28). A subsequent cross-sectional study of 9,387 men by Eisenberg et al. showed that increasing Charlson comorbidity indices 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 (29).

ONCOLOGIC DISEASE

It is well known that cancer and its treatment can impair male fertility (30). However, there is also a growing body of evidence in support of a link between male infertility and risk of developing malignant disease. Perhaps the most thoroughly investigated association is between infertility and testicular cancer. There are several representative studies, including a Danish cohort study looking at more than 32,000 men over a 30-year period, which noted that low sperm concentration, decreased sperm motility, and poorer sperm morphology were each independently associated with an increased incidence of testicular cancer (31). Furthermore, a large American multicenter cohort study of more than 51,000 infertile couples found that known male-factor infertility increases the risk of developing testicular cancer by nearly threefold (32). Another American study used commercial insurance claim data to compare a cohort of 76,000 infertile men with an age-matched control group of 760,000 men, as well as a group of 112,000 vasectomized men presumed to be fertile, and found that the group of infertile men had higher rates of testicular cancer as well as all cancer types, including non-Hodgkin lymphoma (33). Although the mechanistic links between male infertility and testicular cancer require more elucidation, hypothesized mechanisms include genetic, developmental, and environmental etiologic factors, as previously discussed.

A theoretical link between infertility and prostate cancer is less well established, with conflicting data in the existing literature. A 2010 retrospective cohort study looking at 22,562 Californian men who had undergone fertility testing demonstrated that men with infertility were not at an overall increased risk of developing prostate cancer, although a subset analysis did show that infertile men had an increased risk for developing high-grade prostate cancer compared with age-matched control men (34). Conversely, a 2016 retrospective cohort study of 20,433 men who underwent semen analysis found no association between infertility and prostate cancer risk (35), and a nested Swedish case-control study of 445 prostate cancer patients actually reported lower odds of developing prostate cancer in infertile men (36).

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 (37). A 2016 retrospective cohort study of 12,889 men who underwent semen analysis, matched with 12,889 fertile control men, revealed that first-degree relatives of the men who underwent semen analysis had a 52% increased risk of testicular cancer compared with the first-degree relatives of the fertile control men. In addition, first- and second-degree relatives of men with confirmed azoospermia were found to have a significantly increased risk of thyroid cancer compared with the relatives of the control

men (38). 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 men's siblings, as well as specifically a threefold risk of acute lymphoblastic leukemia, compared with the siblings of fertile men (39). Although the origins of these familial associations are again unclear, shared genetics or environmental exposures provide plausible mechanisms. Given the epidemiologic relevance to family members, in addition to the subfertile men themselves, these familial associations warrant additional investigation.

CARDIOVASCULAR DISEASE

An association has been suggested between male infertility and cardiovascular disease as well. 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 and the risk of cardiovascular disease with the use of data from the National Institutes of Health–American Association of Retired Persons Diet and Health Study and found that childless men had an increased risk of death from cardiovascular disease during the study period (an average of 10.2 years) compared with fathers (40). In this context, however, childlessness serves as an imperfect surrogate for infertility, given that childless men may not necessarily be infertile. In epidemiologic studies, men with varicoceles have also been found to have a higher incidence of heart disease (41), and similarly, although varicoceles may contribute to male infertility, the presence of a varicocele does not necessarily imply infertility. A more recent study used insurance claim data to determine the incidence of chronic medical conditions in infertile men. The study demonstrated that men diagnosed with male-factor infertility were at increased risk of developing ischemic heart disease compared with a comparison group of men who had merely undergone fertility testing and a second comparison group of men who had undergone vasectomy and were thought to be likely fertile (42).

There are also data suggesting a potential association between male infertility and hypertensive disease. Previous work has demonstrated that hypertensive men have reduced testosterone levels compared with normotensive men (43, 44). A more recent study found hypertensive men to have lower seminal volume, sperm count, and sperm motility compared with men without the diagnosis of hypertension, although the use of antihypertensives, which have been linked to seminal parameter impairments, was noted to be a potential confounder (45).

OTHER CHRONIC MEDICAL DISEASE

Because an apparent global decline in semen quality over the past half-century (46) has paralleled a burgeoning obesity epidemic, an increasing number of studies have sought to clarify the relationship between male infertility and the metabolic syndrome, a constellation of conditions including obesity, insulin resistance, and dyslipidemia. Given the already established increase in prevalence of oligospermia or azoospermia associated with obesity (24), further work has suggested that lipid concentrations may negatively affect semen parameters, because higher serum levels of total cholesterol and phospholipids have been associated with poorer sperm morphology (47). Other studies have identified an increased prevalence of infertility in men with type 2 diabetes mellitus (48), as well as increased risk of incident diabetes among those diagnosed with male-factor infertility (42).

Recently, a nationwide Danish cohort study of more than 24,000 men diagnosed with male-factor infertility revealed that infertile men had higher risks of both prevalent and incident multiple sclerosis compared with a reference group of fertile men (49). Given the suspected autoimmune nature of the pathogenesis of multiple sclerosis, a subsequent epidemiologic study used insurance claim data to assess for a relationship between male infertility and autoimmune disease, finding that a cohort of infertile men had a higher risk of developing incident rheumatoid arthritis, psoriasis, multiple sclerosis, Graves disease, and autoimmune thyroiditis compared with a cohort of vasectomized, presumed fertile, men and/or a group of age-matched control men (50). Although the mechanism of the proposed association between infertility and autoimmunity remains unclear, there is some suspicion that androgens may play a protective role against autoimmunity, which may be compromised in the setting of hypogonadism (51).

Newer research has cast a light on male infertility as a predictor of hospitalization as well. A recent Danish study of 4,712 men evaluated for infertility and then followed until first hospitalization, death, or study's end found that decreased sperm concentration, total sperm count, and sperm motility were associated with increased rates of all-cause hospitalization. Specifically, sperm concentration <15 million/mL was clearly associated with an increased risk of being hospitalized (52). As with previous 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 et al. examined a large Danish cohort and reported no effect modification based on lifestyle, fertility, health, and socioeconomic status suggesting a biologic explanation for the association between infertility and hospitalization (53).

Mortality

Finally, in light of the associations between male infertility and chronic disease, researchers have sought to explore a potential link between infertility and mortality. Initially, 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, though subgroup analysis suggested a possible association among older members of the cohort (54). However, given that the study was limited to subjects who lived in post–World War II Germany, the generalizability of the results remains questionable. Since then, two large-scale cohort studies have independently suggested that impaired semen quality is associated with increased risk of mortality. Jensen et al. 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, up to a threshold of 40 million/mL. Mortality was also found to decrease in a dose-response manner as sperm motility, morphology, and semen volume increased (55). A subsequent American cohort study of more than 11,935 men evaluated for infertility 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: Men with two 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 $<1\%$ (56).

CONCLUSION

A review of the existing literature suggests that semen quality and male fertility may be fundamental biomarkers of overall health and could serve as harbingers for the development of comorbidity and mortality. 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. 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 elucidate the potential mechanisms and to further clarify the relationship between male infertility and overall health.

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