Chapter 64
Is male reproductive dysfunction a window on general male health?

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Approximately 15% of all couples are infertile with a male factor in around 50% of cases. Importantly, there is a growing body of evidence suggesting that male factor infertility (MFI) (conventionally defined as men with impaired spermatogenesis, Chapter 32) may be a potential biomarker for overall health, as it has been associated with the development of cancer. In addition, disorders such as diabetes, metabolic syndrome, and obesity have been detected at a higher rate among patients with MFI. Furthermore, other studies provide data on a link between infertility and cardiovascular disease (CVD). Moreover, large population studies suggest that there is a higher mortality risk for patients diagnosed with MFI. While the etiology of the association between health and fertility is uncertain, investigators have hypothesized genetic, epigenetic, developmental, and health/lifestyle-related factors.

Infertility and Cancer Risk

Multiple studies have investigated the prevalence of malignancies among infertile patients. One of the first associations explored was testicular germ cell tumors (TGCTs) in men with carcinoma in situ of the testis. Early results were confirmed by a meta-analysis of case-control studies that found a relative risk (RR) of 2.8 (95% CI: 1.16-6.72) for testis cancer among patients with infertility. Larger case-control studies using national registry data confirmed this evidence both in European and US populations. Richiardi et al. (2004) observed a lower risk of testicular cancer for men who have fathered children and Baker et al. (2005) observed that men with testis cancer were less likely to have fathered children compared to controls and they were more likely to be diagnosed with infertility. Others demonstrated an association between semen quality and testis cancer risk in a study of over 30,000 Danish men. In a multicenter study including 51,461 couples recruited from 15

centers in California showed that patients with male factor infertility had a threefold higher risk of testis cancer. Similar results were obtained in a recent retrospective study matching 20,443 men who underwent semen analysis with 20,443 fertile controls, showing that men with semen alterations had an increased risk of testis cancer with a hazard ratio (HR) of 3.3 as compared to controls.

Other male specific cancers have also been explored. The association between MFI and prostate cancer has conflicting data. While some authors reported a higher risk of prostate cancer, others failed to find a significantly higher risk of being diagnosed with prostate cancer using cohort studies. A meta-analysis including eleven studies showed a significantly lower risk of prostate cancer among childless men (using fatherhood as a surrogate for fertility). Importantly, a recent study by Boeri et al. observed that infertile men have higher prostate-specific antigen (PSA) values compared to fertile men. A meta-analysis reported that MFI is associated with an increased risk of both testicular (pooled RR: 2.03) and prostate cancer (pooled RR: 1.68) after comparing four studies (161,634 men) for testicular cancer and four studies (183,950 men) for prostate cancer. Besides urogenital malignancies, other types of cancer have been also associated with MFI; a US cohort demonstrated that patients with MFI have a 49% higher risk for being subsequently diagnosed with any cancer as compared to fertile men, including melanoma, prostate, testis, bladder, thyroid and hematological malignancies. Another study suggested a "dose response" relationship in MFI severity by demonstrating a higher risk of cancer in men with azoospermia compared to those with oligospermia.

Infertility and Metabolic Alterations

In addition to malignancies, other chronic diseases have linked semen quality and male reproductive function. The association between obesity and MFI has been observed in several studies. In a study investigating 26,303 patients by assessing the time to pregnancy, the risk of subfertility was 36% higher among obese compared to normal-weight men. These observations were confirmed by a larger European study in which the association between body mass index (BMI) and semen parameters has been also reported. In a meta-analysis including twenty-one studies, Sermondade et al. (2013) investigated the effect of BMI on sperm quality and demonstrated a significant association between BMI and

abnormal sperm count. Insulin resistance and diabetes mellitus (DM) may also affect male fertility. A meta-analysis including twelve observational studies evaluating the effect of DM on seminal parameters of patients screened for fertility, showed a 14% decrease in the percentage of motile cells among patients with DM compared to healthy controls. Finally, in a large prospective trial including thirty nine thousand subjects from the Danish national IVF register, 1.6% of men developed DM during follow-up. Importantly, the risk was significantly and progressively higher for patients with oligospermia, azoospermia, and aspermiacompared to fertile men. Indeed, the data suggest a common pathogenic background between diabetes and MFI.

In a recent study, slmost one in two primary infertile men presented with a triglycerides/glucose index (TyG) suggestive of insulin resistance showing worse clinical, hormonal, and semen parameters. In addition, abnormal lipid profiles have been observed among infertile men. The LIFE study (Eisenberg et al., 2015) showed that total cholesterol levels were associated with a decreased semen volume, while increased free cholesterol and phospholipid levels were associated with sperm structural and morphological abnormalities. Importantly, both male and female serum-free cholesterol concentrations were associated with increased time to pregnancy. Metabolic syndrome (MS), defined as the presence of three or more of the following risk factors: abdominal obesity, elevated fasting glucose, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and elevated blood pressure, has been associated with MFI. Lotti et al. investigated the metabolic profile of 351 men with MS; of them, 27 (7.75%) were diagnosed with MS. Patients with MS had a lower rate of normal semen morphology. In addition, Ventimiglia et al. suggested a hormonal etiology and identified lower levels of total testosterone, sex-hormone-binding globulin, and inhibin-B in men with MS.

Infertility and Overall health

Both retrospective and longitudinal studies have investigated the role of MFI in overall men's health and mortality. Salonia et al. performed a case-control study including 344 European men with a diagnosis of MFI and 293 age-comparable fertile men using the Charlson Comorbidity Index (CCI) to objectively quantify the burden of patients' comorbidities. Infertile men had significantly higher CCI scores compared to fertile men. Interestingly, longitudinal studies

confirm the association between comorbidities and MFI. Data from the US show that among men with a diagnosis of MFI, the risk of developing subsequent comorbidities was significantly higher. Specifically, the risk of cardiovascular disease, diabetes, and also pathological habits such as alcohol abuse, was significantly higher in the infertile group. In addition, Latif et al. reported the hospitalization rates among 4712 infertile men was significantly associated with semen quality in a dose dependent fashion.

Infertility and Mortality

Male infertility has also been associated with mortality. In a large cohort of Danish men, a linear association btween semen quality (i.e. sperm motility and morphology) and the risk of death was identified. Importantly, the association was present for men with and without children. A US group evaluated nearly twelve thousand men and identifed an association with semen quality and mortality whereby men with at least two semen abnormalities had a two fold higher risk of death.

In contrast, a Swedish study did not identify an associaiton between male infertility and mortality. However, the most recent metaanalysis, does show that male infertility and impaired semen quality are associated with mortality risk. Recent studies suggest that the underlying mechanisms may include various developmental, hormonal, and environmental factors. For example, epigenetic alterations may lead to global changes in protien expression, which may impact spermatogenesis as well as other organ systems leading to the development of comorbidities affecting the health trajectory and thus male overall survival.

Summary

The recent literature supports the hypothesis that male infertility is a proxy of the overall male health status (both current and future). Several studies have linked MFI to an increased risk of testicular cancer. In addition, prostate cancer, melanoma, bladder, thyroid, and hematological malignancies have also been linked to a higher risk among infertile men. Large cohort studies have found a link between diabetes, metabolic abnormalities, and testicular function. Infertile men also appear to have a higher chance of acquiring cardiovascular disorders. A strong link has been discovered between semen anomalies and the overall burden of comorbidities,

as well as overall mortality. The fundamental pathophysiological relationship between infertility and other comorbidities is uncertain, but genetic, epigenetic, environmental, or developmental are leading theories.

Suggested reading

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