ORIGINAL ARTICLE: ANDROLOGY

Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data

Michael L. Eisenberg, M.D.,[a] Shufeng Li, M.S.,[b] Mark R. Cullen, M.D.,[c] and Laurence C. Baker, Ph.D.[d]

[a] Departments of Urology and Obstetrics/Gynecology, [b] Departments of Urology and Dermatology, [c] Department of Internal Medicine, Stanford University School of Medicine, Stanford, California; and [d] Department of Health Research and Policy, Stanford University, Stanford, California and National Bureau of Economic Research, Cambridge, Massachusetts

Objective: To determine the incidence of chronic medical conditions of men with infertility.
Design: Retrospective cohort study.
Setting: Not applicable.
Patient(s): Subjects contained within the Truven Health MarketScan claims database from 2001 to 2009.
Intervention(s): Not applicable.
Main Outcome Measure(s): The development of chronic medical conditions including hypertension, diabetes, hyperlipidemia, renal disease, pulmonary disease, liver disease, depression, peripheral vascular disease, cerebrovascular disease, heart disease, injury, alcohol abuse, drug abuse, anxiety disorders, and bipolar disorder.
Result(s): In all, 13,027 men diagnosed with male factor infertility were identified with an additional 23,860 receiving only fertility testing. The average age was 33.1 years for men diagnosed with infertility and 32.8 years for men receiving testing alone. After adjusting for confounding factors, men diagnosed with male factor infertility had a higher risk of developing diabetes (hazard ratio [HR] 1.30, 95% confidence interval [CI] 1.10–1.53), ischemic heart disease (HR 1.48, 95% CI 1.19–1.84), alcohol abuse (HR 1.48, 95% CI 1.07–2.05), and drug abuse (1.67, 95% CI 1.06–2.63) compared with men who only received infertility testing. Similar patterns were identified when comparing those with male factor infertility to vasectomized men. The association between male factor infertility and later health outcomes were strongest for men with longer follow-up.
Conclusion(s): In this cohort of patients in a national insurance database, men diagnosed with male factor infertility had a significantly higher risk of adverse health outcomes in the years after an infertility evaluation. These findings suggest the overall importance of men's reproductive health and warrant additional investigation to understand the association and identify interventions to improve outcomes for these patients. (Fertil Steril® 2015;■: ■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Male infertility, fertility, diabetes, ischemic heart disease, oligospermia, azoospermia

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/eisenbergm-incident-chronic-disease-male-infertility/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Up to 15% of couples in the United States are unable to conceive after 12 months of trying and are labeled infertile with a male factor identified in 50% of cases (1, 2). Although assisted reproductive technology (ART) may result in excellent live birth rates, the implications for the subfertile father remain uncertain. In addition to procreation, a man's reproductive fitness may also reflect his somatic fitness, and, impaired fertility may be a harbinger of medical diseases in men. Although studies in the United States and Europe have demonstrated increased mortality rates among infertile men with impaired semen parameters, investigations into more proximal end points are few (3, 4). Despite the prevalence of male factor infertility, little is known about the risks of adverse outcomes later in life. The few studies that do exist focus on oncological outcomes (5-9).

Danish investigators linked impaired semen quality to a nearly threefold higher risk of testis cancer in men in the years after an infertility evaluation (5). The US investigators have replicated this finding, and currently the link between infertility and testis cancer is well established (6). Prostate cancer has also been studied, with some (7, 8) but not all (9)

Received August 7, 2015; revised November 4, 2015; accepted November 5, 2015.
M.L.E. holds stock in and is an advisor to Sandstone Diagnostics. S.L. has nothing to disclose. M.R.C. has nothing to disclose. L.C.B. has nothing to disclose.
Reprint requests: Michael L. Eisenberg, M.D., Male Reproductive Medicine and Surgery, Departments of Urology and Obstetrics/Gynecology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, California 94305-5118 (E-mail: eisenberg@stanford.edu).

Fertility and Sterility® Vol. ■, No. ■, ■ 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.11.011

reports suggesting a higher risk of prostate cancer in childless or infertile men. However, to explain the inverse relationship between semen quality and mortality, it is likely that other nononcological morbidities may arise (3, 4). Such a relationship is challenging to study given the rarity of adverse health among men of reproductive age and the lack of national registries to track reproductive and health outcomes. More data on male factor infertility patients and their longitudinal outcomes are essential to understand their risks for adverse outcomes and develop potential preventative interventions.

This study aimed to determine whether men evaluated for infertility have a higher rate of adverse health outcomes in the years after a diagnosis of male factor infertility. To test this hypothesis, we used data from a large commercial insurance claims database from which a sample of patients with a diagnosis or treatment of infertility can be selected and longitudinal health outcomes measured. We assessed the association of male factor infertility with the development of future adverse health conditions.

MATERIALS AND METHODS

Patients

We analyzed subjects contained within the Truven Health Marketscan Commercial Claims and Encounters database. This database provides information from adjudicated and paid insurance claims filed for the care of privately insured individuals with employment-based insurance through a participating employer. Marketscan provides claims data on 77 million covered lives since 1996. This study used data from 2001 through 2009. The number of individuals represented in the database varies over time; the more recent years of the data contain more than 30 million covered lives. Institutional Review Board approval was not required for the analysis of a deidentified national data set.

We focus on a cohort of likely infertile men, identified by the presence on inpatient or outpatient claims of an infertility diagnosis code (International Classification of Diseases, 9th edition, Clinical Modification [ICD9] 606.x). Further subclassifications of male factor infertility (e.g., azoospermia, oligospermia) were separately analyzed. We recorded the first date of a relevant diagnosis as the index date.

A comparison group of men who underwent fertility testing was assembled based on diagnosis and procedural coding (current procedural terminology) for fertility testing or semen analysis (89300, 89310, 89320, 89321, 89322, 89325, 89329, 89330, 89331, V26.21). Given the variable infertility coding and reimbursement practices in the United States, we attempted to be as broad with our definition as possible. As with the male factor infertility group, we recorded the first date of a relevant diagnosis or procedure code as the index date.

In addition, a comparison group of men with claims containing a diagnosis of vasectomy counseling (V25.09, V25.2, V26.52) or procedure code for vasectomy (current procedural terminology 55250 or 55450) was assembled, as this group should include few or no infertile men (10). Men in this group were assigned an index date as the earliest date of a claim with a vasectomy diagnosis or procedure code. For all groups, men were required to have enrollment in a plan covered by the database for at least 1 year before and 1 year after the index date.

As a cancer diagnosis and treatment can lead to infertility and later adverse health, men with any claim with a diagnosis code for cancer before the index date or within 1 year after the index date were excluded (ICD9 140–209, excluding skin squamous cell, skin basal cell, and noninvasive cancers) (11). Men observed before the index date, or within 1 year after, to have other prevalent comorbidities included in the outcome analysis (i.e., hypertension, diabetes, hyperlipidemia, renal disease, pulmonary disease, liver disease, depression, peripheral vascular disease, cerebrovascular disease, heart disease [ischemic and other], injury, alcohol abuse, drug abuse, anxiety disorders, and bipolar disorder) were also excluded. Subjects were required to be enrolled in a plan covered by the database for at least 1 year preceding the index date, and for more than 1 year after the index date. Subjects were required to be between the ages of 18 and 50 years on the index date.

For each man in the cohort, the number of outpatient visits after the index date was ascertained based on the presence of claims with current procedural terminology codes indicating new and follow-up office visits, consultations, or preventative medicine encounters. Medical comorbidities were determined based on ICD9 codes on any claim and included obesity (278.0) and smoking (305.1, V1582).

Outcome Ascertainment

Health outcomes were identified using diagnosis codes on inpatient and outpatient claims. We chose common health conditions and identified men with codes indicating the presence of specific diseases: hypertension (ICD9 401–405), diabetes (250), hyperlipidemia (272.0–272.4), renal disease (580–588), chronic pulmonary disease (490–496), liver disease (570–573), depression (296.2, 296.3, 298.0, 300.4, 309.1, 311), peripheral vascular disease (440–443), cerebrovascular disease (430–438), ischemic heart disease (410–414), other heart disease (420–429), injury (800–959), alcohol abuse (291.0–291.3, 291.5, 291.8, 291.81, 291.89, 291.9, 303.00–303.93, 305.00–305.03, V113, 303.x), drug abuse (292.0, 292.82–292.89, 292.9, 304.00–304.93, 305.20–305.93, 648.30–648.34, 304.x), anxiety disorders (293.84, 300.0, 313.0), and bipolar disorder (296.0, 296.4–296.8).

Statistical Analysis

Men accrued at-risk time beginning 1 year after their index dates until medical diagnosis or their final day of the final year of enrollment in a health plan included in the MarketScan database. The first year was excluded as a queried medical diagnosis within this time period was an exclusion criteria.

We calculated morbidity incidence rates in our cohorts per 1,000 person-years. We then compared the risk of health outcomes in men diagnosed with male factor infertility to