The Epidemiology of Male Infertility

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KEYWORDS

- Epidemiology • Fertility • Research • Treatment • Diagnosis

KEY POINTS

- The goal of epidemiologic research is to describe and interpret patterns of disease occurrence in populations in order to generate knowledge that can be used to prevent and/or treat disease.
- The epidemiology of male infertility is difficult to study for well-described reasons:
  - Male infertility is not a reportable disease.
  - Male infertility is diagnosed and treated in the outpatient clinical setting.
  - Infertility care is often paid for out of pocket and, therefore, may not be noted on insurance billing.
  - Frequently, the empiric treatment of male factor infertility involves assisted reproductive technology (in vitro fertilization) that primarily treats the female partner.
- The true nature of male infertility incidence remains elusive and the prevalence has been weakly estimated in heterogeneous studies.
- Equally perplexing is the assertion of a global decline in male infertility, with many contradictory studies leading to significant debate.
- One consistency throughout this review of literature is that male infertility is variable, with a multitude of influencing factors (race, country, geography, and unique at-risk groups), many of which need further study to better characterize them.
- Future, large-scale, prospective epidemiologic studies may help physicians bridge these gaps in understanding male infertility.

INTRODUCTION

Understanding the occurrence of disease in a population is important because it allows both quantifying and qualifying the burden of disease. Gaining such an understanding allows for societal preparedness, provides direction to scientists, and allows health care providers to counsel patients appropriately. Recently, infertility has been designated as a disease according to the Americans with Disabilities Act. This represents a difference from prior thinking, wherein infertility was deemed a disorder of inconvenience and its treatment considered elective. In contrast, a disease is defined as any deviation from or interruption of the normal structure or function of any part, organ, system, or combination thereof of the body that is manifested by a characteristic set of symptoms or signs. Based on this definition, male infertility meets these criteria.

The purpose of this review is to integrate understanding of epidemiology and infertility. A primer on epidemiologic science is provided and an example disease presented for which the design of epidemiologic investigations is readily apparent.

Key features are then described of infertility that limit epidemiologic investigation and a survey of available data on the epidemiology of infertility provided. Finally, the work that must be completed to move this area of research forward is proposed and what the epidemiology of infertility may be able to teach 20 years from now described. Lastly, with this new perspective of "infertility as a disease," improvements in public health that may be gained through improved understanding of the epidemiology of male infertility are envisioned.

EPIDEMIOLOGY

The goal of epidemiologic research is to describe and interpret patterns of disease occurrence in populations in order to generate knowledge that can be used to prevent and/or treat disease. A majority of epidemiologic studies are based on the concept of identifying all cases of a disease in a defined population at risk. These disease cases are then studied in relation to the base population, from which they arose, in an effort to better understand the condition, generally for therapeutic purposes.[1]

   To better understand the power of epidemiologic research, it is useful to imagine a fictitious, prototypic disease, Disease Z (DZ). Imagine that several decades ago a physician was at a community hospital when he identified a patient with a unique set of symptoms and signs that led to severe respiratory failure requiring hospitalization. The patient had a circular rash on his chest unlike any the doctor had ever seen. This initially seemed an isolated case of disease but, over the next 3 months, the same physician cared for several more patients with respiratory disease of identical quality, all with the circular rash. The doctor described this case series in the *Miscellaneous Journal of Disease*, where he noted the pathognomonic finding of a circular rash, and he gave it the name, DZ. As a result of his publication, cases of DZ began being reported across the country with subsequent publication of several descriptive analyses from different hospitals. Doctors began to suspect that DZ accounted for more than 20% of patients who were hospitalized for acute respiratory failure. Because of the frequency, severity, and life-threatening nature of DZ, the Centers for Disease Control and Prevention (CDC) instituted a requirement that each case of DZ be reported to state public health authorities. No case of DZ escaped recognition due to the need for hospitalization and the unambiguous findings that made the diagnosis. The cause of DZ remained unclear and various therapies were trialed, including antibiotics, antifungals, and antiviral therapies;

however, no one treatment seemed superior to another and patients with DZ did uniformly poorly, often never regaining normal pulmonary function. Two years after the first patient was identified with DZ, a researcher in Boston identified 51 patients hospitalized with DZ in a single city over a 1-year period. He compared these individuals with a second group of 290 patients, hospitalized in the same locations with routine viral or bacterial (non-DZ) pneumonia. His research team systematically reviewed the hospital records and, when necessary, interviewed the patients, their families, and their doctors. They compared the patients by age, race, occupation, socioeconomic status, and place of residence. They also compared patients by their other medical illnesses, medications, and their lifestyle habits, including tobacco smoking, alcohol consumption, and dietary habits. In doing so, they investigated no fewer than 45 potential risk factors as part of the same basic research design: studying each factor required just gathering more information about each subject. Furthermore, the information needed on these cases of DZ and the controls without DZ generally concerned events that had already happened by the time of data collection; therefore, the study could be completed quickly. As a result of this study, 2 factors, X and Y, were found associated with DZ, and patients with DZ had 3 and 4 times the exposure to X and Y, respectively, compared with those without DZ. When the research performed an analysis that grouped individuals by their race, it seemed that the association between X and Y and DZ was far more pronounced in patients of Asian descent relative to other patients. These findings prompted another group of doctors to treat their patients with DZ with a drug (Drug A) that was known to counter the effects of X and Y, and early success was reported in several observational studies. These strong associations also prompted the National Institutes of Health to sponsor a DZ prevention and treatment trial. This randomized controlled trial was specifically oversampled for Asian Americans and assigned one group to Drug A and the other to placebo. Among those individuals treated with Drug A, no cases of DZ developed compared with those not treated, in whom 10% developed DZ.

   The story of DZ could go on further; however, it is clear from this narrative how epidemiologic research has the power to alter the future of DZ:

- It can identify the occurrence of disease in a base population.
- It can acknowledge an increase incidence in disease over time.