Prevalence, Definition, and Classification of Infertility

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2.1 Definition

Infertility is defined by the World Health Organization (WHO) as "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse" [1]. Infertility can also be defined on the basis of demographic considerations, such as "an inability of those of reproductive age (15–49 years) to become or remain pregnant within 5 years of exposure to pregnancy" [2] or as "an inability to become pregnant with a live birth, within 5 years of exposure based upon a consistent union status, lack of contraceptive use, non-lactating and maintaining a desire for a child" [3]. The WHO also defines infertility from an epidemiologic perspective: "women of reproductive age (15–49 years) at risk of becoming pregnant (not pregnant, sexually active, not using contraception and not lactating) who report trying unsuccessfully for a pregnancy for 2 years or more." No definition considers male infertility as a specific condition, and in only one, contained in the 5th edition of the WHO *Laboratory Manual for the Examination and Treatment of Human Sperm*, has the male factor been cited: "Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in 1 year. The male partner can be evaluated for infertility or subfertility using a variety of clinical interventions, and also from a laboratory evaluation of semen" [4]. In this statement, reference is made to the need for a comprehensive evaluation of the infertile male.

Once considered a disorder of inconvenience, infertility has been classified as a disease in the US regulatory Americans with Disabilities Act [5]. Indeed, infertility in women was ranked the fifth highest serious global disability (among rural populations younger than 60 years) [6]. This change of view also applies to men. A disease is any deviation from or interruption of the normal structure or function of any

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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 [7] and thus should accordingly, be considered a disease.

2.2 Epidemiology

While most studies agree that infertility affects approximately 15–20 % of all couples [8–11], data relating to male infertility are more uncertain. An epidemiologic study of male infertility in fact presents a clinical problem because fertility is a couple-related concept and male fecundity (i.e., his biological capacity to reproduce) is a component of the fertility rate. Both male and female partners make an independent contribution to a couple's fertility, but the outcomes of fertility are only fixed in terms of pregnancy rate or births. It is often difficult to determine which partner makes the greatest contribution to a couple's disease, and this difficulty is a feature of infertility, in which there are no pathognomonic findings to confirm a diagnostic certainty. This difficulty is also an important limitation of epidemiologic studies, in which the male factor is often undervalued and underestimated.

Epidemiologic studies of male infertility are also severely limited by several other factors. First, traditionally the couple's infertility is addressed by evaluating the woman while male diagnostics is often confined to a semen analysis. Semen quality and quantity are the most widely used biological markers of male fertility and are a source of essential information in assessing the fertility of a couple, but they correlate with indices of subfertility, such as time to pregnancy (TTP), in addition to sexual activity and several other conditions [12]. Semen analysis is poorly predictive of the male fertility status, mainly giving information about the status of the male genital tract and, thus, only indirect indications of potential male fertility. Moreover, semen analysis is an operator-dependent examination and has a high coefficient of variability [13]. Classification of the male condition of fertility/infertility based on the seminal characteristics is an influential factor that limits the understanding of the problem. Furthermore, male infertility is not a specific disease subject to documentation as is, for example, a prostate cancer, which is easily detectable within large-scale databases. In addition, it is usually evaluated and treated in the private outpatient setting, and clinical data are not stored in the public health system databases. Therefore, quantifying the actual burden of the male component is often impossible. The consequence is a lack of data with which to track diagnoses and treatments of a disease, and difficulty in quantifying its causes and frequency. Another factor limiting the understanding of the epidemiologic problem, and which contributes to the loss of data related to male infertility, is the frequent use of empiric treatments of male factor infertility, such as the in vitro fertilization (IVF) that primarily treats the female partner. In general, IVF programs require that an exact cause is assigned for the woman, whereas the male factor is classified only as present or not present. When a male cause is reported, it is almost always based only on seminal data without undertaking a clinical assessment, making data partial and generic [14, 15].

2.3 Incidence

The majority of studies examining the incidence and prevalence[1] of male infertility have been conducted in specific geographic regions. In these studies, the incidence of male factor infertility varied considerably depending on the region considered. For example, a study conducted in Siberia reported female and male factors to account for 52.7 % and 6.4 %, respectively [10], whereas a Nigerian study revealed a high prevalence of male infertility [16]. In this study, male factor infertility was estimated at 42.4 % whereas female factors were estimated at 25.8 %. In 20.7 % of couples, both partners were affected. Sexual promiscuity and sexually transmitted diseases (and inadequate treatment) have been implicated in the high rate of male factors [16]. Epidemiologic studies are numerous but, even considering all the data available today, none is able to define the incidence of male infertility. Male factor infertility can vary widely based on geography (e.g., Siberia vs Nigeria) and inherent risk factors. Evaluating existing literature, a component of male factor infertility may range widely, from 6 to 50 %, with many groups estimating 30–50 % [17–20]. Perhaps the only consistent aspect found in the scientific literature is that male infertility is variable with a multitude of contributory factors (race, country, geography, socioeconomic variables, environmental and occupational exposures, the fertility of the partner, and so forth), many of which require further research to be better characterized. To understand the approximation of these data it should be re-emphasized, however, that the true extent of male infertility is probably underestimated because of the frequent lack of assessment of the male in the diagnostic workup of infertile couples. Eisenberg et al. [21] have evaluated the frequency of evaluation of male infertility using data from the National Survey of Family Growth, and have found that 18–27 % of men in infertile couples were not evaluated. Overall, these data suggest that male factor infertility is a significant component of global infertility and needs better quantification, using population-based studies conducted on a large scale, to help physicians fill these gaps in understanding.

2.4 Classification

The nosology of male infertility, despite the growing attention it receives from medical research, is still difficult to define. On the one hand a growing burden of the male component of the infertile couple is described, with studies reporting a decline in male fertility over the years [22–25]. On the other hand, except for some specific causes of infertility such as cryptorchidism and genetic causes, other infertility factors, such as varicocele or genitourinary tract infections, often remain hypothetical and are not investigated. Male infertility therefore continues to be classified as being due to poor semen quality (oligozoospermia, asthenozoospermia, or teratozoospermia alone or in

[1] Incidence is defined as the number of new cases of a disease in a specific population at risk over a specific period of time. Prevalence is defined as the total number of cases of disease (both old and new) present in a specified population at a single point in time.

combination) of unknown causes, which does not contribute to increased knowledge about the etiology [26]. A correct clinical evaluation of the infertile male would, instead, identify an infertility factor in 60–70 % of cases (Table 2.1). In 30–40 % of cases, no cause of male infertility can be found; these men, affected by oligoasthenoteratozoospermia syndrome, might be defined as having idiopathic male infertility.

Table 2.1 Male infertility causes and associated factors, and percentage of distribution in 10,469 patients

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
All	100 %	11.2 %
Infertility of known (possible) cause	42.6	42.6
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm autoantibodies	3.9	–
Testicular tumor	1.2	2.8
Others	5.0	1.2
Idiopathic infertility	30.0	13.3
Hypogonadism	10.1	16.4
Klinefelter syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	<0.1	0.3
Others	0.8	0.8
Late-onset hypogonadism	2.2	–
Constitutional delay of puberty	1.4	–
General/systemic disease	2.2	0.5
Cryopreservation due to malignant disease	7.8	12.5
Testicular tumor	5.0	4.3
Lymphoma	1.5	4.6
Leukemia	0.7	2.2
Sarcoma	0.6	0.9
Disturbance of erection/ejaculation	2.4	–
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (congenital bilateral absence of vas deferens)	0.5	3.1
Others	0.8	1.9

From Jungwirth et al. [27] and Thonneau et al. [26]

Table 2.2 Classification and distribution of the causes of male infertility

Pretesticular	5–10 %
Testicular	65–75 %
Post-testicular	10–20 %

Table 2.3 Main factors associated with male infertility

Cryptorchidism
Genetic causes
Varicocele
Testicular tumors
Testicular trauma
Genitourinary tract infections (testis, epididymis, prostate, seminal vesicles)
Iatrogenic causes (surgery, chemotherapy, radiotherapy)
Systemic diseases
Twisting of the spermatic cord

Table 2.4 Main risk factors associated with male infertility

Age
Lifestyle
Cigarette smoke
Substances abuse (alcohol, cannabis derivatives, opioids)
Sedentary lifestyle/obesity
Scrotal temperature (clothing, underwear, occupational exposure to heat, regular sauna)
Exposure factors and/or toxic environmental/occupational
Family history of infertility and/or recurrent poliabortivity

When we consider male factor infertility, we imply a series of possible causal factors divided into pretesticular causes (inadequate stimulation of the testis by gonadotropin), testicular causes (diseases of the testis), and post-testicular causes (seminal tract obstructions, ejaculatory disorders, erectile dysfunction) (Table 2.2). As almost none of the causes can be considered a definitive factor of infertility, it is preferable to define each condition as a male infertility associated factor whenever a clinical evaluation of the infertile male is performed Table 2.3). In addition, many risk factors are associated with a worsening of semen quality (Table 2.4), which is attracting great attention and should be considered in the process of collecting the medical history, but for which, at present, the scientific evidence is not sufficiently strong.

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