

Epidemiology and aetiology of male infertility

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Infertility is a common problem, affecting perhaps one couple in six, the majority of whom now seek medical care. Although diagnostic problems make it difficult to establish the extent of the male partner's contribution with certainty, a number of studies suggest that male problems represent the commonest single defined cause of infertility. The World Health Organization has proposed a scheme for the diagnostic classification of male infertility, based upon a standardized approach to clinical assessment and to the assessment of semen quality. Some of these classifications are now controversial, and many are descriptive, rather than aetiological. Increasingly, the importance of occupation, environmental and particularly genetic factors in the causation of male infertility is being recognized.

Key words: aetiology/epidemiology/infertility/male

Infertility

Infertility is commonly defined as the failure of conception after at least 12 months of unprotected intercourse (Rowe *et al.*, 1993). It is clear that it is a common problem affecting young couples, and equally clear that it results in considerable distress for those couples affected. The feelings experienced by infertile couples encompass anger, depression, anguish, denial, guilt, shame, inadequacy, shock, isolation and embarrassment (Wright *et al.*, 1991).

Epidemiology of infertility

The first study of the epidemiology of infertility was published in Scotland in 1866 by Matthews

Duncan. His book, *Fecundity, Fertility and Sterility* (Duncan, 1866) was the first, and until recently the only, population-based study of infertility (Templeton, 1992). Regrettably, there are few national data on the prevalence of infertility. Census-type data indicate the proportion of women remaining childless, but such data are confounded by the (unknown) proportion of voluntary childlessness. Thus while the proportion of women remaining childless in successive birth cohorts has tended to rise (Botting, 1992), the rate of voluntary infertility has also shown marked changes, and some workers have concluded that any apparent increase in infertility in the 1960s and 1970s is more likely to have been due to voluntary, rather than involuntary factors (Poston and Kramer, 1983). For example, in the US in the 1920s and 1930s, voluntary childlessness was common, perhaps accounting for 25–40% of childless couples, but after this time, voluntary childlessness became less common, re-emerging only in the 1960s (Templeton, 1992). Hence substantial difficulties exist in assessing the prevalence of infertility, given that large-scale population-based surveys are rare (Greenhall and Vessey, 1990; Thonneau and Spira, 1990), one notable exception being the US National Survey of Family Growth (NSFG) (Mosher and Pratt, 1991). Surveys of 'infertility' will include both those who are sterile and those who have impaired fecundity, and several authors have suggested that infertility should be categorized into those who have become pregnant following a subfertile episode, 'resolved' infertility, and those whose infertility remains 'unresolved' (Greenhall and Vessey, 1990; Mosher and Pratt, 1991). There are wide variations in the published

data on the prevalence of resolved infertility, with rates of 5–14% being cited for resolved primary infertility, and 3–12% for resolved secondary infertility. For unresolved infertility, rates of 3–9% and 3–7% have been quoted for primary and secondary infertility respectively.

Prevalence of infertility

The observed prevalence of infertility will evidently depend on the definition used. Whilst common clinical practice, and many studies, are based on a definition of failure to conceive after 12 months of unprotected intercourse, many authorities, based upon the distribution of fecundity observed in a 'normal' population, have defined infertility as the failure of a couple to conceive after 2 years of unprotected regular coital exposure (Anonymous, 1996). It should be clear, however, that such a definition of 'infertility' serves to obscure the true complexity of the clinical situation. In reality, those couples who fail to achieve a pregnancy within 12–24 months include those who can be considered sterile (and who will never achieve a spontaneous pregnancy) and those who are more properly termed subfertile, and who have reduced fecundability (probability of achieving a pregnancy within one menstrual cycle) and hence a prolonged time to pregnancy (Joffe *et al.*, 1993; Joffe and Li, 1994a,b). Most studies of the prevalence of infertility are either clinic-based (Hull *et al.*, 1985b; Thonneau *et al.*, 1991) or based on population samples ((Rachootin and Olsen, 1982; Hirsch and Mosher, 1987; Johnson *et al.*, 1987; Page, 1989; Greenhall and Vessey, 1990; Templeton *et al.*, 1990; Schmidt *et al.*, 1995). Clinic-based studies would be expected to underestimate the prevalence of subfertility, since they include only couples who have sought medical help. Similarly, studies which use a longer duration of infertility (2 years) might be expected to report lower prevalence rates (Templeton *et al.*, 1990). It is perhaps surprising, therefore, that most studies published recently are in broad agreement on the prevalence of infertility (Figure 1) with a figure of 14% of all couples being typical. Clinic-based studies will also tend to report a majority of couples presenting with primary infertility, whereas population-based studies indicate an equal or

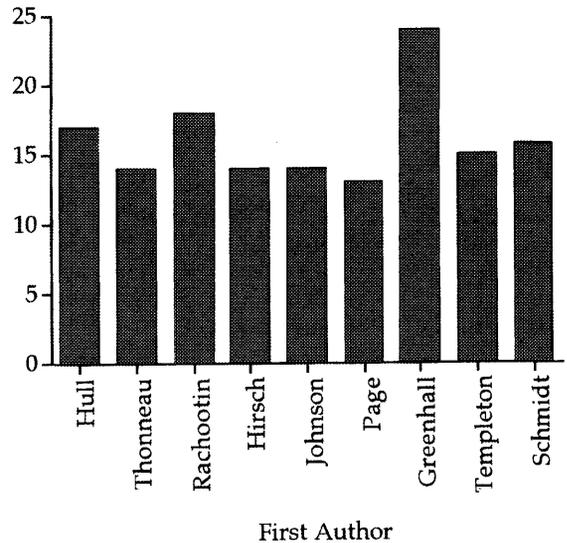


Figure 1. Recent studies reporting prevalence rates of infertility (percentage of couples). (Rachootin and Olsen, 1982; Hull *et al.*, 1985b; Hirsch and Mosher, 1987; Johnson *et al.*, 1987; Page, 1989; Greenhall and Vessey, 1990; Templeton *et al.*, 1990; Thonneau *et al.*, 1991; Schmidt *et al.*, 1995).

greater proportion of couples with secondary infertility (Hirsch and Mosher, 1987; Templeton *et al.*, 1990), reflecting differences in the uptake of medical services between the two groups. It is noteworthy that the prevalence of infertility amongst couples trying to conceive ('at risk') will be higher than the population figure. For example Schmidt *et al.* (1995) in a study of 2861 women in Denmark found a population prevalence of 15.7%, yet of those women who had attempted to conceive, 26.2% had experienced infertility.

Changes in prevalence

The evidence for changes in the prevalence of infertility is difficult to interpret. Census data in the USA have suggested an overall increase in the prevalence of infertility during the last three decades compared to the previous five (Hastings and Robiinson, 1974; Jacobson *et al.*, 1988), although there would not appear to have been any overall change from 1965 to 1988 (Mosher and Pratt, 1991). The USA NSFG has observed that while there may have been a substantial increase

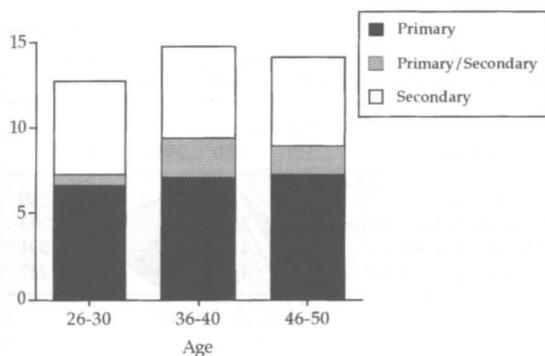


Figure 2. Prevalence of infertility (% of study population) among three age cohorts of women from a defined geographical area. Prevalence of primary, primary or secondary or secondary infertility, each of 2 years duration (data from Templeton, 1992).

in the numbers of women presenting with impaired fecundity, this is almost entirely explained by the phenomenon of delayed childbearing, together with the entry of the 'baby boom' cohort into the relevant 25–44 year reproductive age cohort, with the proportion of women with infertility remaining unchanged (Mosher and Pratt, 1991). Similarly, there has been no cogent evidence of an increase in the prevalence of infertility in Europe. Perhaps the best analysis of this problem is that undertaken in a defined geographical area of Scotland by Templeton *et al.* (1992). They surveyed 2295 women aged between 26 and 50, and have found no change in the pattern of infertility, whether primary or secondary, resolved or unresolved (Figure 2). What has changed is the extent to which infertile couples choose to seek medical help. In their study, Rachootin and Olsen (1982), suggested that the majority of infertile women at that time chose not to seek medical care. A later US study found that overall only 50% of women with subfertility sought medical help, women with primary infertility being twice as likely to seek medical help as women with secondary infertility, and there were marked demographic differences between those women with secondary infertility who sought care and those who did not (Hirsch and Mosher, 1987). More recently, Templeton *et al.* (1992) have clearly documented the increase that has occurred in the proportion of infertile couples seeking medical advice, with <10% of infertile couples not now seeking help. (Figure 3).

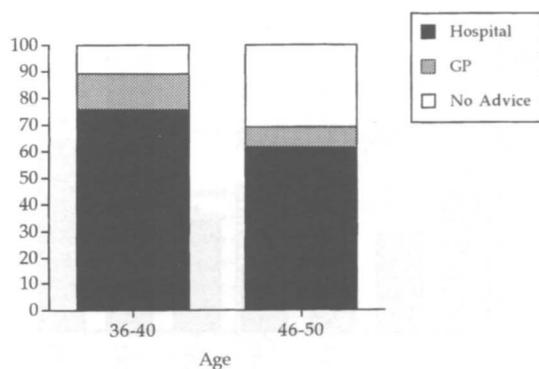


Figure 3. Percentage of infertile women in two age cohorts seeking medical advice. GP = general practitioner. (Data from Templeton *et al.*, 1992).

Epidemiology of male infertility

While infertility is relatively common, it is very difficult indeed to establish the relative contribution of the male partner, given the profound difficulties which exist in the accurate diagnosis of male infertility. Most studies that have attempted to evaluate the aetiology of infertility have used the conventional criteria of semen quality, promulgated by the World Health Organization (WHO, 1980, 1987, 1992b). Although of great importance, these criteria are of limited diagnostic value (Irvine and Aitken, 1994)(Irvine and Aitken, 1994), and a significant proportion of men with normal conventional criteria of semen quality will be infertile because of defects in sperm function (Aitken *et al.*, 1982a, 1991) while a significant number of men with abnormal semen quality will have normal sperm function (Aitken *et al.*, 1982b, 1985). Very few studies on the epidemiology of male infertility have used functional, as opposed to descriptive, diagnostic criteria (Hull *et al.*, 1985b). Nevertheless, one common theme to emerge is that, using the available diagnostic techniques, male factor infertility is, in many studies, the commonest single diagnostic category (Figure 4) (Collins *et al.*, 1983; Cates *et al.*, 1985; Hull *et al.*, 1985a; Haxton and Black, 1987; Randall and Templeton, 1991; Thonneau *et al.*, 1991; Schmidt *et al.*, 1995).

Diagnosis of male infertility

As was suggested above, a major obstacle to meaningful study of the epidemiology of male

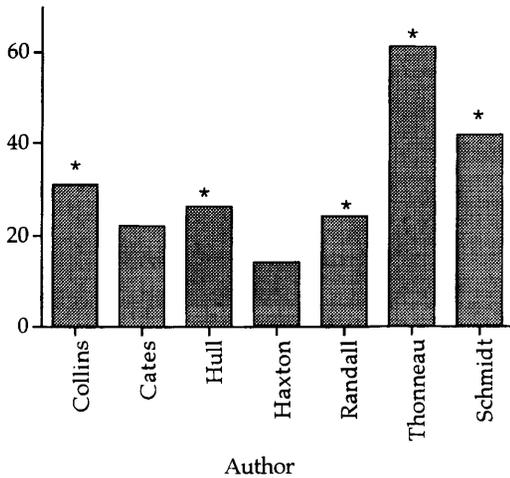


Figure 4. Frequency of 'male factor infertility' as a percentage of in couples investigated for infertility. (Data from Collins *et al.*, 1983; Cates *et al.*, 1985; Hull *et al.*, 1985a; Haxton and Black, 1987; Randall and Templeton, 1991; Thonneau *et al.*, 1991; Schmidt *et al.*, 1995). *Studies in which male factor was the single largest diagnostic category.

infertility is the difficulty in accurate diagnosis of the presence or absence of a problem. Traditionally, the diagnosis of male infertility is based upon the conventional semen profile, constructed according to recognized guidelines (WHO, 1992b; Van den Eede, 1995). This profile incorporates information on the volume of the ejaculate, the concentration of spermatozoa, their motility and their morphological appearance. Unfortunately, a number of significant shortcomings limit the diagnostic value of this assessment. Marked inter-ejaculate variability is a major problem in the assessment of human semen (Scwartz *et al.*, 1979; Mallidis *et al.*, 1991), and many aspects of the profile are subjective, and have not traditionally been subjected to quality control, with disconcerting evidence of inconsistency between laboratories (Neuwinger and Nieschlag, 1990; Cooper *et al.*, 1992; Matson, 1995). Although WHO has promulgated a range of 'normal' values, these are not evidence-based, either in terms of their diagnostic value, nor in terms of their relationship to the normal fertile population. As a consequence, many couples with 'unexplained' infertility can be shown to have defective sperm function when appropriately sensitive assays are used, and some couples with subnormal conventional semen parameters have

Table I. Limits of normal semen quality in 4291 samples from a group of normal volunteer donors in Edinburgh

Measurement	Percentiles				n
	5th	10th	90th	95th	
Volume (ml)	1.1	1.5	5.2	6.0	4289
Concentration ($\times 10^6/\text{ml}$)	16	26	196	241	4283
Motility (overall %)	34	41	74	78	4291
Morphology (normal %)	39.8	43.6	84	87	237

normal sperm function (Irvine and Aitken, 1986; Glazener *et al.*, 1987; Anonymous, 1996). It is perhaps more logical for individual laboratories to define their own normal ranges, with reference to their normal fertile population.

For example, in Edinburgh, a review of the semen quality of 4291 semen samples provided by a panel of normal semen donors (2017 of which came from a group of recently proven fertility) revealed that the 5th percentiles were: for ejaculate volume 1.1 ml, sperm concentration $16 \times 10^6/\text{ml}$, overall motility 34%, and normal morphology 40% (by old WHO criteria) (Table I). Hence approximate 'normal' values of $20 \times 10^6/\text{ml}$ for concentration, and 40% for motility and morphology would seem appropriate for this population. Translating this to the clinical situation, a similar review of the quality of the first sample from 3317 new couples attending a general infertility clinic in Edinburgh revealed (Figure 5) that 4.2% were azoospermic, whilst only 8% had measurable sperm concentrations $< 5 \times 10^6/\text{ml}$, often regarded as the severely oligozoospermic range. Similarly, 5.9% of new patients had no motile sperm in their ejaculate, 3.1% had $< 1 \times 10^6$ motile sperm, and 4.8% had $1-5 \times 10^6$ motile sperm in their first ejaculate.

Causes of male infertility

Notwithstanding the difficulties in diagnosis outlined above, the WHO has proposed a scheme for the diagnostic classification of the male partner of the infertile couple (Rowe *et al.*, 1993; Table II). This approach is of enormous value as a basis for standardization, and for comparative multi-centre studies. However, many of the male diagnostic categories are of a descriptive nature (e.g. idiopathic oligozoospermia) or of controversial clinical

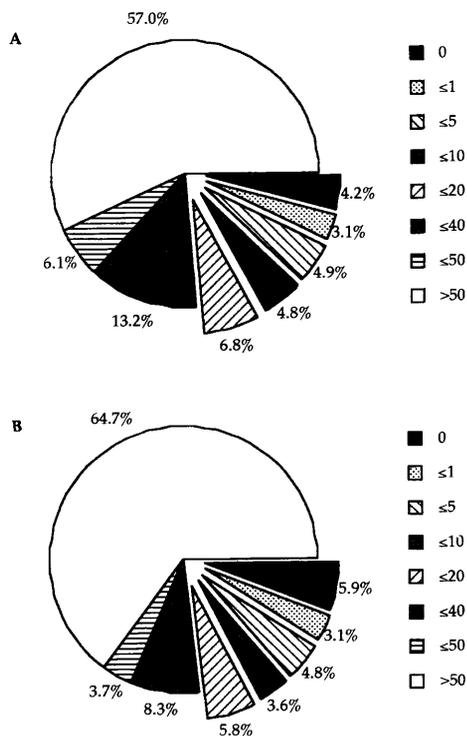


Figure 5. Distribution of semen quality amongst 3317 new couples attending a general infertility clinic. (A) Sperm concentration $\times 10^6/\text{ml}$; (B) total numbers of motile spermatozoa per ejaculate $\times 10^6$.

Table II. Diagnostic categories for the male partner of an infertile couple according to the World Health Organization

No demonstrable cause	Systemic causes
Idiopathic oligozoospermia	Endocrine causes
Idiopathic asthenozoospermia	Iatrogenic causes
Idiopathic teratozoospermia	Congenital abnormalities
Idiopathic azoospermia	Acquired testicular damage
Obstructive azoospermia	Varicocele
Isolated seminal plasma abnormalities	Immunological infertility
Sexual or ejaculatory dysfunction	Male accessory gland infection

relevance (e.g. male accessory gland infection). Moreover, recent advances in our understanding of the causes of male infertility, particularly in the area of genetic problems, mean that this classification is now in need of review (Najmabadi *et al.*, 1996; Vogt *et al.*, 1996). The relative frequency of the major diagnostic categories are shown in

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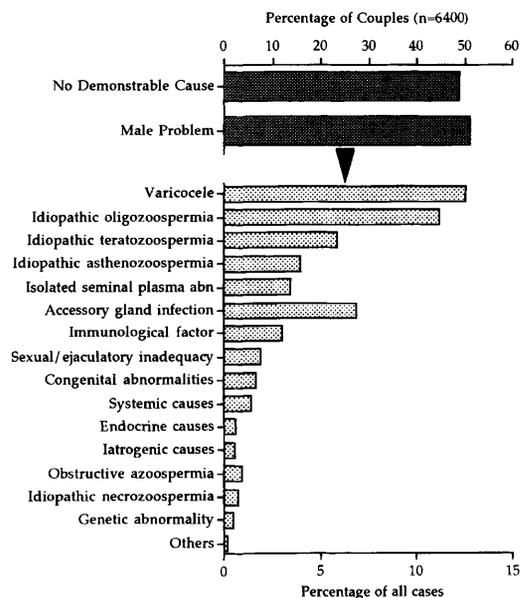


Figure 6. Proportion of couples with a male diagnosis, and distribution of diagnoses in 6400 couples investigated according to World Health Organization guidelines. The largest grouping of male diagnoses, accounting for 25.3% of cases, was of idiopathic aetiology. (Data from Comhaire *et al.*, 1987).

Figure 6, using data taken from a WHO study of >8500 couples from 33 centres in 25 countries, 71% of whom reached the point of diagnosis (Comhaire *et al.*, 1987). It can be seen that the largest single male 'diagnostic' category was men with seminal abnormalities of unknown cause. Beyond this, varicocele was a relatively common pathology, as was male accessory gland infection; however, systemic, iatrogenic and endocrine causes were very infrequent.

It is important to recognize that a number of general epidemiological factors will have a bearing on a couple's fertility. Examples of this include age, there being clear evidence that the age of the female partner is a major determinant of fertility (Joffe and Li, 1994b; Templeton *et al.*, 1996), although the impact of male age is less certain. Smoking by both partners is highly relevant, there being evidence that smokers have lower sperm concentrations than non-smokers (Joffe and Li, 1994b; Vine *et al.*, 1994, 1996). Occupational, environmental and genetic factors may also be highly relevant and are addressed below.

There can be no doubt that recent advances in assisted conception technology have revolutionized the treatment of couples with male factor infertility (Bonduelle *et al.*, 1996; Silber *et al.*, 1996), and have advanced our understanding of the aetiology of male infertility by drawing attention to the major contribution of genetic factors (Reijo *et al.*, 1995; Najmabadi *et al.*, 1996; Vogt *et al.*, 1996). Paradoxically they have also encouraged a minimalist clinical approach to the diagnosis of men with fertility problems, given the limited range of effective therapeutic options. The dangers of this approach have been discussed (Cummins and Jequier, 1994), in the light of existing concerns over the safety of microassisted fertilization (Cummins *et al.*, 1994; Cummins and Jequier, 1995).

Varicocele

The subject of varicocele has generated controversy amongst the andrological community since the Edinburgh urologist Tulloch (1952) first reported the apparently beneficial effects of treatment. The available evidence certainly suggests that varicocele is a common pathology, and that it is commoner in men with lower sperm counts. In a survey of >10 000 military recruits, a population prevalence of just <10% was observed (Damonte *et al.*, 1984), although prevalence figures of 5–25% have been reported in similar surveys of apparently healthy men (Hargreave, 1994). In contrast, amongst men attending infertility clinics, varicocele affects some 11% of men with normal semen, and 25% of men with abnormal semen (WHO, 1992a). The difficulty has been in establishing with certainty whether or not varicocele affects spermatogenesis, and most importantly, whether or not treatment of varicocele improves fertility, and if so, in which groups of men. It seems clear that varicocele is associated with abnormal semen quality (WHO, 1992a), and while the mechanism of this relationship remains to be established with certainty, abnormal testicular temperature regulation is known to be associated with varicocele (Goldstein and Eid, 1989; Ali *et al.*, 1990), and with impairment in semen quality (Thonneau *et al.*, 1996; Tiemessen, *et al.*, 1996). Whatever the pathophysiology, there is a substantial body of evidence suggesting that varicocele

causes progressive testicular damage (Chehval and Purcell, 1992; Gorelick and Goldstein, 1993; Witt and Lipschultz, 1993), further complicating an assessment of its role in the aetiology of male infertility. Substantial controversy exists, however, over the question of whether or not the correction of varicocele improves fertility, with some evidence in favour of treatment (Laven *et al.*, 1992; Madgar *et al.*, 1995), and some suggesting that it is of no benefit (Baker *et al.*, 1985; Nieschlag *et al.*, 1995). Appropriate randomized controlled trials, with the power to control for confounding variables, are urgently needed, and the publication of the recently completed WHO trial is keenly awaited. In the context of contemporary assisted conception techniques, it is interesting that recent evidence suggests that the presence of varicocele may even reduce the ability of the haploid male gamete to generate embryos when used for micro-assisted fertilization (Sofikitis *et al.*, 1996).

Male accessory gland infection

The second commonest diagnostic grouping in the WHO survey, this is also an area of considerable aetiological controversy. Whilst there is little doubt that overt sexually transmitted disease may damage male fertility, and should be appropriately managed, there is much more doubt about the relevance of sub-clinical infection. Thus it is clear that gonorrhoea is implicated in the aetiology of obstructive azoospermia (Jequier and Holmes, 1984), and that chlamydial infection in the male can lead to tubal infertility in his partner (Weström, 1996). It is much less clear whether subclinical infection in the male is causally associated with infertility (BarChama *et al.*, 1994) and there is no clear consensus on diagnostic criteria (Purvis and Christiansen, 1993). One possible consequence of infection is seminal leukocytosis (Eggert-Kruse *et al.*, 1995) and one consequence of seminal leukocytosis is the excessive generation of reactive oxygen species (ROS) by these cells (Krausz *et al.*, 1992). There is good evidence linking the excessive generation of ROS with male infertility as an aetiological entity in its own right – prospective studies have shown that couples with elevated levels of ROS generation are less likely to conceive either spontaneously, or in the context of in-vitro

fertilization (Aitken *et al.*, 1991; Sukcharoen *et al.*, 1995). Excessive ROS can originate from both abnormal spermatozoa and from contaminating leukocytes (Aitken *et al.*, 1994), and the diagnostic and therapeutic implications of this pathology remain to be fully elucidated (Irvine and Aitken, 1996).

Immunological causes

Suspected immunological infertility was found in some 3% of couples in a WHO survey (Figure 6), on the basis of the finding of $\geq 10\%$ of motile spermatozoa coated with antibody using assays such as the immunobead test (IBT) or the mixed antiglobulin reaction (MAR). Whilst antisperm antibodies are found in perhaps one in six of the male partners of infertile couples, a prevalence which is higher than that for fertile controls, their effect on fertility is hard to determine. Some studies suggest that 'antibody-positive' couples conceive at a lower rate than those without immunological problems (Busacca *et al.*, 1989). Unfortunately, antibodies to sperm surface antigens are also found in fertile control populations, and it is unfortunate that current techniques do not permit the meaningful separation of cases with auto-immunity to biologically relevant epitopes (Paradisi *et al.*, 1995). Given the consensus view that assisted conception is the treatment of choice, this may not now be a clinically relevant issue.

Systemic and iatrogenic causes

Many general medical disorders are associated with male infertility, either directly (e.g. Kartagener's syndrome), indirectly as a consequence of systemic disturbance (e.g. diabetes), or as a consequence of medical or surgical intervention on account of the primary disease. Systemic disorders associated with infertility are listed in Table III, and drugs associated with male infertility in Table IV.

Occupational causes

Data on occupational hazards to male reproduction remain controversial. Exposure to heavy metals such as cadmium, lead, arsenic and zinc has been reported to impair spermatogenesis, although the

Table III. Systemic disorders and diseases associated with male infertility

Congenital disorders

Chromosomal disorders
 Testicular maldescent
 Kartagener's syndrome
 Cystic fibrosis
 Prader-Willi syndrome
 Androgen receptor deficiency
 Coeliac disease

Acquired disorders

Infections
 Mumps
 Tuberculosis
 Gonorrhoea
 Chlamydia
 Syphilis
 Endocrine disease
 Thyrotoxicosis
 Diabetes
 Hepatic failure
 Renal failure
 Pituitary failure
 Neurological disease
 Paraplegia
 Myotonic dystrophy
 Respiratory disease
 Bronchiectasis
 Sinusitis and bronchitis

data are conflicting (Coste *et al.*, 1991; Hu *et al.*, 1992). Certain pesticides and herbicides have more clearly been shown to be toxic to spermatogenesis (Eaton *et al.*, 1986), as have some organic chemicals (Veulemans *et al.*, 1993). The role of occupational exposure to heat remains controversial (Rachootin and Olsen, 1983; Thonneau *et al.*, 1996).

Environmental causes

Data on environmental factors and infertility in the male are also controversial. There would seem to be clear evidence that occupational or environmental exposure to heat will have adverse consequences for spermatogenesis (Mieusset and Bujan, 1995), and will prolong time to pregnancy (Thonneau *et al.*, 1996). There have been many recent data demonstrating that male reproductive health is deteriorating, with evidence of a secular decline in semen quality (Carlsen *et al.*, 1992; Auger *et al.*,

Table IV. Drugs that may be associated with male infertility

Anti-androgens	Spirolactone, cyproterone acetate, Cimetidine, flutamide
Androgen suppressors	Ketoconazole, leuprolide
Oestrogens and hormones	Oestrogen agonists, growth hormone, anabolic steroids
Cardiovascular agents	Propranolol, methyl dopa, digoxin, calcium channel blockers, reserpine, amiodarone, acetylcholinesterase inhibitors
Gastrointestinal tract	Sulphasalazine
Antineoplastic drugs	Cyclophosphamide, Melphelan, Chlorambucil, nitrosoureas, busulphan, methotrexate
Anti-infective agents	Nitrofurantoin, Niridazole, colchicine
Psychoactive drugs	Tricyclic antidepressants, amphetamines, narcotics, major and minor tranquillizers
Others	Phenytoin
Drugs of abuse	Anabolic steroids, alcohol, marijuana, cocaine, nicotine

1995; Irvine *et al.*, 1996), an increase in the incidence of congenital malformation of the male reproductive tract (Lancet, 1985), and an increase in the incidence of testicular cancer (Akre *et al.*, 1996; Bergström *et al.*, 1996). It has been postulated that these changes may be due to perinatal exposure to environmental xeno-oestrogens (Sharpe and Skakkebaek, 1993); however, there is (as yet) no evidence that these agents are having an influence on the prevalence of male infertility.

Genetic causes

Perhaps the most striking advances in our understanding of the aetiology of male infertility in the past decade has been in the area of genetics. Many of the 'systemic' disorders mentioned above and listed in Table III are now understood to have a genetic basis, and as our knowledge of the aetiology of disease expands, this will be increasingly the case. Traditionally, genetic causes of male infertility have been sought at the level of chromosomal abnormalities, with chromosomal abnormalities being detected in between 2.1 and 8.9% of men attending infertility clinics. Chandley, in a study of 2372 men attending an infertility clinic in Edinburgh, found significant abnormalities in 21.5 per 1000 men, significantly different from the rate of 7 per 1000 new born males in the same city (Chandley, 1994). Of these the majority were sex chromosome abnormalities, most commonly being associated with azoospermia. However, it has been recognized for some time that structural anomalies of the Y chromosome, resulting in deletion of the distal fluorescent heterochromatin in the long arm,

are associated with severe abnormalities of spermatogenesis (Chandley *et al.*, 1986, 1989). More recent studies have defined a family of genes on the Y chromosome involved in spermatogenesis (Ma *et al.*, 1993; Reijo *et al.*, 1995), and it has become clear that a little >10% of cases of non-obstructive azoospermia may be due to deletions affecting these genes (Reijo *et al.*, 1996). A proportion of cases of very severe oligozoospermia may have a similar aetiology (Najmabadi *et al.*, 1996; Reijo *et al.*, 1996).

Conclusions

Infertility is a common and distressing condition, and problems in the male partner are the commonest single group of causes. However, the major difficulties which exist in the accurate and meaningful diagnosis of male reproductive dysfunction serve to complicate our understanding of the epidemiology and aetiology of male infertility. This is an important point because correct treatment requires, as its basis, accurate diagnosis. It is to be hoped that the availability of effective treatments, in the form of assisted conception and microassisted fertilization, will not impede efforts to diagnose, understand and ultimately prevent male infertility.

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