Article

Relationship between epidemiological features and aetiology of male infertility as diagnosed by a comprehensive infertility service provider

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Abstract

This study examined the relationship between demographic features and aetiological causes of male infertility. Primary infertility was the presentation in 78% of patients. The incidence of varicocele was the highest (31%), whereas only 4.6% had vasectomy reversal and 7.4% of men were diagnosed with idiopathic infertility. Using the chi-squared test, there was no significant difference in the incidence of different causes of infertility among different ethnic groups (White, African-American, Asian, Hispanic, and other). Furthermore, there was no increased incidence of infertility aetiology with any particular occupation, race, religion, smoking or alcohol intake. In this study population, there was no association between the various risk factors (occupation, smoking, alcohol intake, and race) and the aetiologies of infertility. The proportion of patients diagnosed with idiopathic infertility was significantly less than reported in the literature.

***Keywords**: aetiology, alcohol, demographics, male infertility, race, smoking*

Introduction

Approximately 15% of couples are infertile, and half of these couples are diagnosed with male factor infertility (Sharlip *et al.*, 2002). In the late 1940s, MacLeod performed a series of studies in which he analysed human semen production and its relationship to male fertility. Since then, numerous studies have documented variations in human spermatozoa and their risk factors. In addition to physiological variations, genetic, environmental, lifestyle and psychosocial factors appear to affect sperm production in humans (Sharpe and Franks, 2002). These factors can act by themselves, but they can also interact in a complex manner. However, proving the link between these factors and infertility is difficult, and no conclusive evidence is present in the literature. Therefore, understanding the effect of these factors and their potential interactions may provide new information concerning the physiology of sperm production and variables that may affect this process. However, it is also necessary to design scientifically oriented preventive strategies.

One of the strategies used to assess the importance of and the interplay between different perceived risk factors underlying male infertility is to look at the demographic characteristics of infertile men. Unfortunately, there is a paucity of information in the literature on demographic characteristics of patients attending infertility evaluation in the general population. Available epidemiological studies have either focused on the cost implications of managing male infertility (Hull, 1996; Griffin and Panak, 1998; VanderLaan *et al.*, 1998) or examined the effect of relevant demographic characteristics in isolation, such as occupation and age (Adamopoulos *et al.*, 1996; Zini *et al.*, 2000; Rolf *et al.*, 2002) or lifestyle (Sharpe,

2000). Some studies have considered other risks such as smoking habits (Marinelli *et al.*, 2004) and alcohol intake (Olsen *et al.*, 1997), but none has studied the potential effects associated with a combination of these factors (Marinelli *et al.*, 2004). It is important to study all the relevant demographic characteristics together in a set of infertile patients because this may provide valuable information on the risk factors by eliminating the confounding factors.

This study charts the profile of patients referred to an andrology laboratory for diagnostic purposes within a comprehensive infertility programme in a teaching hospital with services for conventional therapies, as well as a full access to assisted reproductive technologies. The objective was to identify demographic and epidemiological features that may be associated with recognized aetiological causes of male infertility.

Materials and methods

The Cleveland Clinic Foundation's Institutional Review Board approved this study. Medical records of patients who attended the male infertility clinic between 1998 and 2003 (n = 805) were obtained.

Baseline medical data and epidemiological features were charted from these records and entered into an Excel spreadsheet (Microsoft, USA). The following 12 variables were included within the data collection: age, race, marital status, medical insurance coverage, religion, occupation, residence (city/state/country), referral centre (physician), tobacco smoking, alcohol use, aetiology of infertility and type of infertility (primary/secondary). For every patient in the study population, the diagnosis of male infertility was established within the same clinical setting applying a standardized work-up protocol (Rowe *et al.*, 1993). Complete access to all basic and advanced laboratory techniques was available (such as direct and indirect immunobead testing, sperm function tests as well as genetic studies if required) with no financial constraints to diagnose the underlying cause of infertility. Only one primary aetiological cause of infertility was assigned to any one patient. The chosen aetiology may account for any associated conventional abnormalities in sperm parameters [sperm count, motility and normal morphology applying the Tygerberg's strict morphological criteria (Kruger *et al.*, 1987)]. For instance, when abnormal sperm count and motility were encountered in the presence of leukocytospermia, the later was considered the primary cause of infertility. Idiopathic infertility was only diagnosed when there were no detectable abnormalities to account for couples' infertility. This is distinctly different for the narrower use of the word 'idiopathic' to express lack of understanding of the cause of abnormal testicular or sperm function.

Statistical methods

Summary statistics were presented as means and standard deviation. Chi-squared test was utilized to compare the incidence of studied features among subgroups arranged in cross-tables. The presence of significant linear trends was examined even in the presence of non-significant chi-squared test. Data was analysed using inbuilt functions within the Statistical Package for Social Science (SPSS UK Ltd, Chertsey, Surrey, UK).

Results

The mean age of patients was 34.89 ± 7.38 years. Insurance coverage for infertility evaluation was available to 85% of all patients.

Source of referrals

Thirty-one per cent of patients (253/805) were referred by in-house gynaecologists and urologists, 48% (385) by primary healthcare practitioners, 6% (47/805) were self-referral and 15% (120/805) had no documented source of referral.

Dwelling

Sixty-seven per cent of the patients were from the city of Cleveland, 21.8% were from outside the city but within the state of Ohio, and 8.7% were from another state. A small percentage of the patients (2.5%) were from out of the country.

Etiological causes of infertility

Among the study population, 78% presented with primary infertility and 22% with secondary infertility. The distribution of different aetiological causes of infertility among this group of men is given in **Figure 1**. Amongst the aetiologies, the incidence of varicocoele was the highest (32.3%). Only 7.5% of men were diagnosed with idiopathic infertility.

Occupation

Of the 805 patients, occupation was documented in 792. Of these patients, 24.5% (194/792) were classified as professionals, 37.4% (296/792) were in administrative/sales/services occupations, 23.9% (189/792) labourers, 5.4% (43/792) military and law enforcement, 1.6% (13/792) students and 7.2% (57/792) others. There was no significant difference in the incidence of different causes of infertility among different occupational groups (χ^2 = 48.47) with no evidence of a significant linear trend (r = –0.017846).

Ethnicity and religion

Of the 805 patients included in this study, 783 had a documented ethnicity (**Table 1**): white (82%), African-American (7%), Asian (2%), Hispanic (2%) and 'other' (7%). Of all the patients, 85% had medical coverage for their infertility evaluation. The proportion of patients who were covered by health insurance was similar among different ethnic groups (χ^2 = 14.3). There was no significant difference in the incidence of different causes of infertility among different ethnic groups (χ^2 = 28.45) with no evidence of significant linear trend (r = –0.046794). The religious affiliation was known in 459 patients. Of these, 299 patients (65.1%) were mainstream Christians, 44 (9.6%) Muslims, 15 (3.3%) Jewish, 5 (1.1%) Hindu, and other religious groups

6 (1.3%), and 90 (19.6%) had no religious affiliation. There was no significant difference in the distribution of different causes of infertility among different religious affiliations (χ^2 = 30.345).

Alcohol consumption

Alcohol consumption with reference to different diagnoses (**Table 2**) was examined. Alcohol consumption was unknown for 76 patients. Of the remaining 729 patients, 264 (36.2%) stated that they never consumed alcohol, 417 (57.2%) patients occasionally consumed alcohol, and 35 (4.8%) were habitual drinkers. The incidence of the different aetiological causes of infertility in these subgroups of patients was similar (χ^2 = 37.164911) with no evidence of significant linear trend (r = 0.016657).

Smoking habits

Smoking habits in reference to different diagnoses (**Table 3**) were also examined. The smoking habit was unknown for 75 patients. Of the remaining 730 patients, 499 (68.4%) stated that they never smoked, 105 (14.4%) patients smoked ≤20 cigarettes per day and 48 (6.6%) smoked >20 cigarettes per day. The incidence of the different aetiological causes of infertility in these subgroups of patients was similar (χ^2 = 27.3041) with no evidence of significant linear trend (r = –0.000506).

Effect of combined smoking and alcohol consumption

To study the effect of combined smoking and alcohol consumption as the underlying cause of infertility, the 109 individuals who engaged in both lifestyle behaviours (group 1) and the 200 individuals who never smoked and never consumed alcohol (group 2) were identified. Primary infertility was encountered in 85% (93/109) in group 1 and 81% in group 2 (161/200). The proportions of men presenting with abnormal sperm parameters of count, motility and normal morphology were similar in both groups (40.4 and 45% respectively). Overall, the incidence of the different aetiological causes of infertility in these two groups of patients was similar (χ^2 = 10.05), with no evidence of significant linear trend (χ^2 for linear trend = 3.202273).

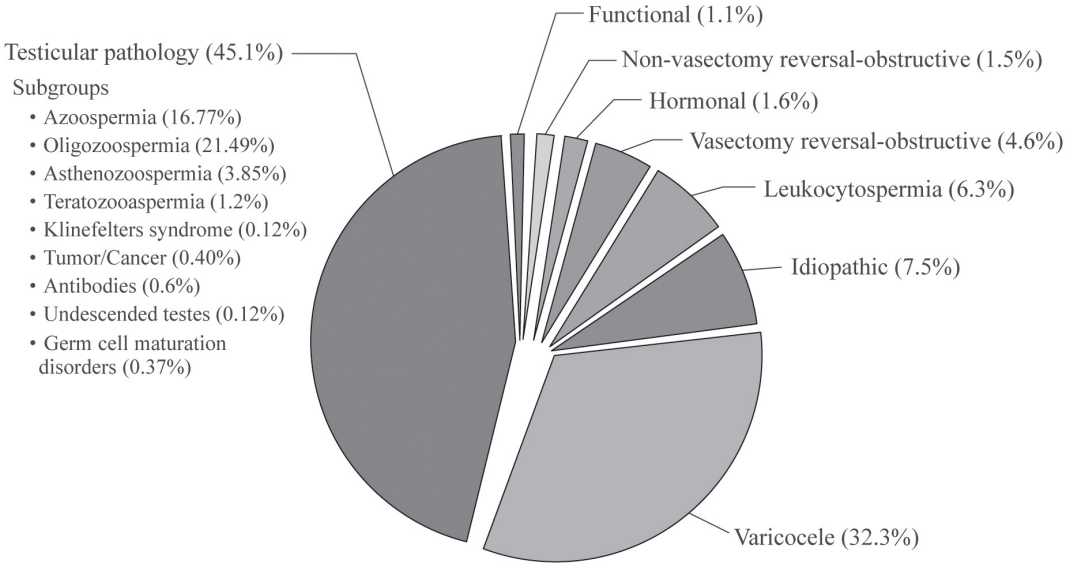

Figure 1. Distribution of different aetiologies in a population of infertility patients attending tertiary care male infertility clinic during 1998–2003. Varicocoele and different testicular pathologies were the largest aetiologies among these patients. Functional = erectile or ejaculatory dysfunction; idiopathic = idiopathic infertility.

Table 1. Incidence of different causes of infertility among different ethnic groups.

Aetiology	*Race* *White (%)*	*Black (%)*	*Asian (%)*	*Hispanic (%)*	*Other (%)*	*NA*	*Total population*
Hormonal	1.88 (12/640)	1.82 (1/55)	–	–	–	–	13
Varicocele	31.88 (204/640)	34.55 (19/55)	30.77 (4/13)	16.67 (2/12)	38.10(24/63)	7	260
Testicular pathology	44.06 (282/640)	41.82 (23/55)	38.46 (5/13)	75.00 (9/12)	53.97(34/63)	10	363
Obstructive (vasectomy reversal)	5.31 (34/640)	3.64 (2/55)	–	–	–	1	37
Obstructive (non-vasectomy reversal)	1.72 (11/640)	1.82 (1/55)	–	–	–	–	12
Functional	1.25 (8/640)	1.82 (1/55)	–	–	–	–	9
Idiopathic	7.97 (51/640)	9.09 (5/55)	7.69 (1/13)	8.33 (1/12)	–	2	60
Infection	5.94 (38/640)	5.45 (3/55)	23.08 (3/13)	–	7.94 (5/63)	2	51

NA = data not available; functional = erectile or ejaculatory dysfunction; idiopathic = idiopathic infertility.

Table 2. Alcohol intake, and incidence of infertility among men with different aetiologies.

Aetiology	*Alcohol intake* *No H/O alcohol use%*	*Occasional %*	*Habitual %*	*H/O alcohol use %*	*NA*	*Total population*
Hormonal	1.52 (4/264)	1.92 (8/417)	–	–	1	13
Varicocele	35.98 (95/264)	30.46 (127/417)	37.14 (13/35)	30.77 (4/13)	21	260
Testicular pathology	45.45 (120/264)	45.32 (189/417)	40 (14/35)	46.15 (6/13)	34	363
Obstructive (vasectomy reversal)	0.76 (2/264)	5.76 (24/417)	5.71 (2/35)	–	9	37
Obstructive (non-vasectomy reversal)	1.89 (5/264)	1.68 (7/417)	–	–	–	12
Functional	1.14 (3/264)	1.44 (6/417)	–	–	–	9
Idiopathic	7.95 (21/264)	6.00 (25/417)	14.29 (5/35)	23.07 (3/13)	6	60
Infection	5.30 (14/264)	7.43 (31/417)	2.86 (1/35)	–	5	51

Functional = erectile or ejaculatory dysfunction; H/O = history of; idiopathic = idiopathic infertility; NA = data not available.

Table 3. Smoking and incidence of infertility among men with different aetiologies. Group 1 = none; group 2 = more than 1 pack/day (%); group 3 = less than 1 pack/day (%); group 4 = H/O smoking (%); group 5 = chewing tobacco (%); group 6 = substance abuse (%).

Aetiology	*Smoking* *Group 1 %*	*Group 2 %*	*Group 3 %*	*Group 4 %*	*Group 5 %*	*Group 6 %*	*NA*	*Total population*
Hormonal	1.80 (9/499)	–	1.90 (2/105)	1.61 (1/62)	–	–	1	13
Varicocele	32.06 (160/499)	37.5 (18/48)	30.48 (32/105)	38.71 (24/62)	42.86 (6/14)	–	20	260
Testicular pathology	46.29 (231/499)	45.83 (22/48)	41.90 (44/105)	37.10 (23/62)	57.14 (8/14)	–	35	363
Obstructive (vasectomy reversal)	2.81 (14/499)	2.083 (1/48)	7.62 (8/105)	8.06 (5/62)	–	–	9	37
Obstructive (non-vasectomy reversal)	2.00 (10/499)	2.08 (1/48)	0.95 (1/105)	–	–	–	–	12
Functional	1.20 (6/499)	2.08 (1/48)	0.95 (1/105)	–	–	50 (1/2)		9
Idiopathic	7.62 (38/499)	4.17 (2/48)	8.57 (9/105)	8.06 (5/62)	–	50 (1/2)	5	60
Infection	6.21 (31/499)	6.25 (3/48)	7.62 (8/105)	6.45 (4/62)	–	–	5	51

Functional = erectile or ejaculatory dysfunction; idiopathic = idiopathic infertility; NA = data not available.

Discussion

So far as is known, this is the first study to report collectively on the relationship between the incidence of various aetiological factors of male infertility and occupation, race, religion, smoking and alcohol intake. The results showed that occupation, race, smoking and alcohol intake were not associated with any significant differences in the distribution of different aetiological causes of male infertility.

In addition, the overall incidence of different aetiological causes of male infertility was in agreement with previous reports (Lewis-Jones and Gazvani, 1997; Irvine, 1998), with two notable exceptions. First, the proportion of patients diagnosed with either post-vasectomy obstruction or idiopathic infertility was markedly lower than reported in the literature. This low percentage may be attributed to patients directly undergoing assisted reproduction to resolve their infertility within a setup offering a comprehensive range of therapies. Second, the proportion of patients diagnosed with idiopathic infertility generally varies between 20 and 30% (Irvine, 1998). In the present study population, this figure was significantly lower at 7.4%. It is the authors' experience that having a specialized andrology laboratory with in-house reproductive endocrinologist and urologist is important in establishing the correct diagnosis of couples seeking help, thus reducing the number of patients categorized with idiopathic infertility.

The aetiological classification of male infertility included leukocytospermia, which is believed to be detrimental to sperm function and its fertilizing potential (Aziz *et al*., 2004). The use of 'infection' as an aetiological cause of infertility was also intentionally avoided, because this may manifest as obstruction or leukocytospermia. The term 'infection' may also be confused with other systemic viral infections, which are detrimental to spermatogenesis.

Unlike the established classification of aetiological causes of female infertility, the same has not been standardized for male infertility. Currently, there are different ways of classifying the causes of male infertility. The first method is descriptive and utilizes conventional sperm and semen parameters (Adeniji *et al*., 2003). The second method uses various anatomic approaches (Pontonnier and Bujan, 1993). Finally, a systemic classification of all causes leading to male infertility has also been described (Lewis-Jones and Gazavani, 1997). The World Health Organization has proposed a scheme for the diagnostic classification of male infertility based upon a standardized approach to clinical assessment and assessment of semen quality. Some of these classifications are now controversial, and many are descriptive rather than aetiological (Irvine, 1998). The aetiological classification adopted in this study is clinically oriented and practice-based, built on current understanding of male infertility (**Figure 1**).

Reduced sperm count or motility was considered to be the cause of infertility only when these findings were not thought to be secondary to other pathology. In the light of recent information, it is possible that abnormal genetic control of sperm production is the underpinning cause of suboptimal sperm parameter in at least some of these cases (Barri *et al*., 2005). The rapid evolution of understanding of sperm production physiology, its genetic control and the impact of environmental factors (outside and within the testis) should, in time, lead to the formulation of a standardized classification of the aetiological causes of male infertility (Krausz and Sassone-Corsi, 2005; Paduch *et al*., 2005). In the meantime, the present classification can be regarded as a comprehensive and informative categorization of male infertility.

In this study, neither alcohol consumption nor smoking was associated with specific aetiological causes of infertility. The data on the effect of alcohol intake on spermatogenesis are sparse, and show an apparent protective effect of moderate alcohol drinking on sperm parameters probably due to the antioxidant effect of some alcoholic beverages (Close *et al*., 1990; Marinelli *et al*., 2004). In population-based studies, alcohol intake by men was not associated with fecundity (Curtis *et al*., 1997; Olsen *et al*., 1997). However, heavy drinking (>20 units/week) is known to be associated with subfecundity (Hassan *et al*., 2004). Patients diagnosed with alcohol dependency syndrome were found to have poor sperm count and morphology that recovered within 10 weeks of treatment (Kucheria *et al*., 1985; Brzek, 1987).

The literature is conflicting in regards to the effect of smoking on spermatogenesis. This may be due to the fact that the reported studies have different designs. It may also be due to different population susceptibility to smoking. To further complicate matters, accumulating evidence suggests that the effect of smoking on semen parameters may be indirect. Recently, smoking has been associated with increased seminal reactive oxygen species concentrations (Saleh *et al*., 2002), oxidative stress-induced sperm DNA damage (Sepaniak *et al*., 2004), leukocytospermia (Close *et al*., 1990; Trummer *et al*., 2002), and changes in the concentrations of testosterone and prolactin hormones (Trummer *et al*., 2002). Controlling for all these variables becomes essential before any changes in sperm parameters can be attributed to the direct effects of smoking.

A recent literature review noted that none of the studies that considered both alcohol and smoking habits has conducted an analysis of the joint effect of the two exposure factors (Marinelli *et al*., 2004). In the present study, no difference was observed in the distribution of different aetiological causes of male infertility among men who smoked and consumed alcohol and those who did not. This may be explained by the presumed antioxidant effect of alcohol consumption on spermatogenesis. More importantly, the study data have been generated as a result of self-reported life style issues.

The results did not show any difference in the distribution of different aetiological causes of infertility and occupation. There is accumulating evidence that workplace exposure to toxic substances and excessive heat contributes to male infertility (Claman, 2004). Admittedly, the present study did not attempt to ascertain workplace or environmental exposures to toxin. However, the fact that the study did not support this notion may indicate that the effect of subtle environmental factors may only be manifest in certain individuals who are particularly susceptible perhaps due to genetic predisposition. In addition, the results agree with other studies that did not show conclusive evidence for a relationship between male infertility and social class (Coughlin *et al*., 2003).

In conclusion, the demographic characteristics of patients

attending infertility clinic at a tertiary care centre are presented. There was no association between the various risk factors (occupation, smoking and alcohol intake, race and religion) and the aetiologies of infertility. There is evidence that redistribution of patient activity within a comprehensive fertility programme is underway as a result of vasectomy patients availing themselves of assisted reproduction earlier to resolve their infertility. This also may explain the low percentage of patients diagnosed with post-vasectomy obstruction in this study population. In the authors' experience, having a specialized andrology laboratory with in-house reproductive endocrinologist and urologist (male infertility specialist) is important in establishing the correct diagnosis of couples seeking help, thus reducing the number of patients categorized with idiopathic infertility. This shift should be of interest to healthcare planners.

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