Sociodemographic Findings in an Infertile Male Population

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OBJECTIVE: This research aims to identify the sociodemographic features of serious spermatogenetic disorders in infertile males.

STUDY DESIGN: A total of 585 infertile men were eligible. Infertile men with abnormal physical findings were compared to infertile men with normal physical findings. Infertile men with severe spermatogenetic abnormalities (azoospermia and oligoasthenoteratozoospermia) were compared to infertile men with other spermatogenetic disorders.

RESULTS: The majority of the subjects revealed no surgery, chronic disease, trauma, drug use or gonadotoxic exposure that could be related to their infertility. Testicular atrophy which was the most common physical finding, was significantly related to trauma. Subjects with abnormal physical findings were more likely to have severe spermatogenetic abnormalities which were directly correlated to gonadotoxic agents, particularly heat exposure.

CONCLUSION: This study claims that the previously established risk factors which are considered to be associated with infertility might influence less or interfere with male infertility in more subtle ways.

Key Words: Azoospermia, Etiopathogenesis, Male infertility, Spermiogram

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Introduction

According to World Health Organization, infertility affects up to 7%-10% of the general population; that is, one in every six couples is trying to solve their infertility problem. Abnormalities in the male are the sole cause of infertility in approximately 15-20% of childless couples and are an important contributing factor in another 30–40%.[1]

Unfortunately the cause of infertility is never found in almost 17.5% of affected couples and 25% of men, merely demonstrating the fact that mechanisms that direct the reproductive functions in men are still poorly understood.[2] This research aims to identify demographic and medical causes of serious spermatogenetic disorders in an infertile male population.

Material and Method

The present study was approved by The Institutional Review Board and Ethics Committee of Dr Zekai Tahir Burak Women's Health Hospital where the study was carried out. A total of 585 Turkish men presenting with primary infertility who attended to the out-patient clinics of andrology department in the study center between January 2007 and January 2008 were eligible for the research. All participants were informed about the study and their written informed consents were obtained.

Infertility is defined as the inability to conceive despite one-year-long unprotected sexual intercourse. Azoospermia is described as the absence of sperms on standard microscopic examination.[3] Oligoasthenoteratozoospermia is defined by sperm density less than 20 millions/ml, normal sperm morphology and sperm motility less than 50%.[4]

Each participant was questioned in aspects of age, infertility, medical and surgical history, drug use, trauma, occupation, gonadotoxin exposure, smoking, alcohol intake and substance abuse. All subjects were physically examined and their testicular volumes were evaluated by orchiometry.

Testicular atrophy was defined as testis volume less than 10 ml.[2] Semen samples were obtained from each patient by means of masturbation after a three-day-long sexual abstinence, and the ejaculate was fully liquefied. Semen samples were centrifuged at high speed (3000 g for 15 minutes) and the pellets were examined at high magnification (x400). The criteria of World Health Organization for male infertility were used to assess the number, morphology and motility of sperms.[5] In order to confirm the diagnosis of azoospermia, the absence of sperm was documented on at least two separate specimens obtained four weeks apart.

Peripheral venous blood samples of 5 ml were collected and within an hour of sample collection; serum levels of follicle-timulating hormone (FSH), luteinizing hormone (LH), total testosterone and estradiol were measured with specific chemiluminescence assays (Abbott Laboratories, Chicago, IL, USA). The normal ranges of FSH, LH, total testosterone and

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estradiol were accepted to be within 4.60 to 12.40 mIU/ml, 4.00 to 12.00 mIU/ml, 2.80 to 8.00 ng/dl and 10.00 to 60.00 pg/ml respectively.

Infertile men who were diagnosed with abnormal physical findings were compared with infertile men who had normal physical findings. Moreover infertile men with severe spermatogenetic abnormalities (azoospermia and oligoasthenoteratozoospermia) were compared with infertile men who have less severe spermatogenetic disorders or who have normospermia in the same aspects.

Collected data were analyzed by computerized Statistical Package for Social Sciences (SPSS for Windows, Version 11.0, SPSS Inc. USA). Pearson's chi-square and Fisher's exact tests were used to test the relations between demographic and medical features of the patients and their physical findings and spermiogram results. Mann-Whitney test was applied to identify the correlations between physical findings, spermiogram results, hormone levels and duration of infertility. The p values less than 0.05 were considered to be statistically significant.

Results

The mean age of the study population was 32.3 years (range: 24-51 years). The majority of the subjects (90.1%) primary infertility with an average duration of 7.6 years. Approximately half of the subjects (41.1%) had undergone scrotal surgery including orchiopexy, orchiectomy, varicocelectomy and abscess drainage.

The predominance of the subjects (91.4%) had no chronic diseases that could be related to infertility. The rest of the subjects had systemic diseases such as vasculitis (including Behçet's disease and diabetes mellitus), asthma bronchiale, tuberculosis, malignancies (including testis tumor and Hodgkin's disease), and psychiatric disorders. 87.5 % of these patients did not use any medication routinely.

The generality of the participants (98.3%) did not experience any trauma. Although %67.7 of the patients did not show off any occupational risk associated with infertility, 32.3 % of the subjects were found to be exposed to the occupational gonadotoxins including heat, pesticides and other industrial chemicals for an average of 7.4 years. Four out of 585 men were exposed to chemotherapeutics while being treated for Hodgkin's disease.

An important fraction of the participants (34.4 %) had a habit of smoking (one package/day for 13.4 years in average). 7.9% of the subjects regularly consumed alcohol (two glasses/day for 10.1 years in average). Only one subjects claimed abusing hashish for two years.

Physical examination was normal in 32.5% of the study population. Testicular atrophy was the most frequent (53.2%) abnormal physical finding, followed by varicocele accompanied with testicular atrophy (11.8%). Abnormalities in physical examination were significantly correlated with trauma, duration of alcohol consumption and severe spermatogenetic disorders such as azoospermia and oligoasthenoteratozoospermia (Table 1).

Table 1: Clinical Features in Subjects with Normal and Abnormal Physical Findings

	Normal Findings (n=190)	**Abnormal Findings (n=395)**	**p**
Age (years)	34.3 ± 6.7	31.4 ± 5.8	0.88
Primary infertility	171 (90.0%)	356 (90.1%)	0.96
Duration of infertility	7.7± 0.5	7.6± 0.3	0.81
Chronic diseases	17 (8.9%)	33 (8.4%)	0.88
Surgery history	80 (42.1%)	160 (40.5%)	0.80
Trauma history	**1 (0.5%)**	**9 (2.3%)**	**0.04***
Drug use	24 (12.6%)	49 (12.4%)	0.89
Smoking habit	64 (33.7%)	137 (34.8%)	0.86
Duration of smoking (years)	13.4± 1.1	12.9± 0.7	0.88
Alcohol consumption	11 (5.8%)	35 (8.9%)	0.22
Duration of alcohol intake (years)	**13.2± 1.9**	**8.4± 0.9**	**0.03***
Gonadotoxin exposure	60 (31.6%)	129 (32.7%)	0.80
Duration of gonadotoxin exposure(years)	12.1± 1.0	11.6± 0.8	0.79
Duration of occupation (years)	12.6± 1.1	11.8± 0.7	0.58
Azoospermia	**49 (25.8%)**	**217 (54.9%)**	**0.03***
FSH (mIU/ml)	**8.7± 0.6**	**16.9± 0.4**	**0.01***
LH (mIU/ml)	**6.9± 0.4**	**9.2± 0.5**	**0.01***
Total testosterone (ng/dl)	18.3± 7.7	12.7± 3.4	0.06
Estradiol (pg/ml)	30.3± 0.9	30.9± 2.1	0.28

** $p<0.05$ is considered to be statistically significant.*

The spermiogram studies resulted in severe spermiogram disorders (azoospermia and oligoasthenoteratozoospermia) in respectively 45.5% and 38.6% of subjects. Severe spermatogenetic disorders were observed significantly more in subjects with primary infertility, in subjects exposed to gonadotoxins and also in subjects diagnosed with abnormal physical findings. Severe spermiogram disorders are directly correlated with the duration of alcohol intake whereas inversely correlated with duration of infertility (Table 2).

Table 2: Clinical Features in Subjects with Severe and Other Spermiogram Disorders

	†Severe Disorders (n=492)	**Other Disorders (n=93)**	p
Age (years)	31.7 ± 4.3	35.5 ± 2.7	0.66
Primary infertility	**459 (93.3%)**	**68 (73.2%)**	**0.01***
Infertility duration (years)	**6.4 ± 0.6**	**7.9 ± 0.3**	**0.01***
Trauma history	8 (1.6%)	2 (2.2%)	0.44
Chronic diseases	41 (8.3%)	9 (9.7%)	0.88
Surgery history	196 (39.8%)	44 (47.3%)	0.76
Drug use	60 (12.2%)	13 (14.0%)	0.66
Smoking habit	168 (34.1%)	33 (35.4%)	0.88
Duration of smoking (years)	13.6 ± 1.5	12.8 ± 0.6	0.69
Alcohol consumption	38 (7.7%)	8 (8.6%)	0.81
Duration of alcohol intake (years)	13.6 ± 1.8	9.3 ± 1.1	**0.02***
Gonadotoxin exposure	139 (28.3%)	50 (54.1%)	**0.01***
Duration of gonadotoxin exposure(years)	10.5 ± 1.1	12.1 ± 0.7	0.34
Duration of occupation (years)	10.7 ± 1.1	12.3 ± 0.7	0.29
Abnormal physical examination	**358 (72.7%)**	**37 (39.2%)**	**0.01***
FSH (mIU/ml)	**8.6 ± 1.3**	**15.1 ± 0.7**	**0.01***
LH (mIU/ml)	**5.6 ± 0.5**	**8.8 ± 0.4**	**0.01***
Total testosterone (ng/dl)	**24.6 ± 1.7**	**13.4 ± 3.2**	**0.02***
Estradiol (pg/ml)	31.2 ± 1.4	30.7 ± 1.6	0.21

†Severe spermiogram disorders include azoospermia and oligoasthenoteratozoospermia
** $p<0.05$ is considered to be statistically significant*

The mean concentrations of FSH, LH, prolactin, total testosterone and estradiol were computed to be 14.51 mIU/ml, 8.53 mIU/ml, 16.00 ng/ml, 2.82 ng/dl and 30.71 pg/ml respectively. FSH, LH, prolactin, total testosterone and estradiol levels were found to be normal in 58.2%, 63.1%, 98.2%, 76.3% and 97.7% of the participants. Subjects with abnormal physical findings or severe spermatogenetic disorders had significantly higher FSH, LH and lower total testosterone levels when compared to other spermatogenetic disorders.

Discussion

Although fertility in men appears to decline as age increases, the effects of age are much less obvious compared to women.[6] Yet the available evidence indicates that pregnancy rates decrease and time to conception increases as male age increases.[7]

In a study done by Merino et al, sperms with abnormal morphology and percentage of progressive motility were found in patients who are over 40 years of age. However there is a remarkable heterogeneity of semen characteristics within the examined groups, differing from azoospermia to polyzoospermia.[8] Pasqualotto et al proved that sperm concentration and motility decrease and FSH levels increase with age, especially above the age of 45. Thus, the ageing effect should be considered when proposing standard values for semen characteristics in routine semen analysis.[9] However age could be statistically correlated with neither physical findings or spermiogram results in the present study.

Aziz et al diagnosed varicocele in 31% of patients, 7.4% of whom had idiopathic infertility.[10] Ghazzal from Jordan reported that 3.0% of a randomized male population had inguinal hernia; 0.5% had undescended testis; 1.9% had hypospadias; 2.7% had varicocele.[11] Although testicular atrophy was the most frequent (53.2%) abnormal physical finding, the majority of subjects did not reveal any infectious or chronic disease that can be related to testicular atrophy in the present study.

Inguinal hernia repair, renal transplantation, orchiopexy and other types of retroperitoneal and scrotal surgery are associated with risks for unrecognized injury to the neural pathways which might contribute to infertility by causing ejaculatory dysfunction.[12] Although 41.1% of the subjects had undergone genitourinary surgery, surgery was irrelevant to either spermiogram disorders or physical abnormalities.

Many commonly encountered drugs such as anabolic steroids, anti-metabolites, estrogens, testosterone and anti-androgens are potential hazards to male reproduction [13]. Antibiotics including sulfasalazine, erythromycin and tetracyclines and anti-epileptic agents also harm testicular tissue.[14] Chemotherapeutics and especially MOPP (mechlorethamine, vincristine, procarbazine, and prednisolone) regimen used to treat Hodgkin's disease diminish male fertility by interfering with testicular functions.[15] Drug use was uncorrelated with neither physical abnormalities or spermiogram disorders.

A modest increase in scrotal temperature can adversely affect spermatogenesis, and a febrile illness can result in transient but dramatic decrease in sperm density and motility.[16] Environmental sources of heat, including tight-fitting underclothing, hot baths and sedentary occupations might decrease fertility.[17]

The human data on the relationship of semen quality with phthalate and pesticide exposure are limited and do not currently allow for a definitive conclusion.[18] Adult exposure to persistent organochlorine pollutants and hydrocarbons at high ranges might be associated with impaired sperm motility.[19] Exposure to heavy metals, especially lead, in transport and communication industry can interfere with spermatogenesis.[20]

Lee et al. reported no close correlation between male infertility and either occupation or age.[21] Although the study was conducted in a Chinese infertile male population similar to that of the present study in aspects of age, duration of infertility and spermiogram disorders; occupational heat exposure was significantly more common in Turkish men with severe spermatogenetic disturbances. It may be concluded that young men working in food, transport, agriculture and heavy industries are under utmost risk for severe spermatogenetic disorders as they are continuously exposed to heat.

Nicotine is proved to be a potent pro-oxidant to the biological samples like spermatozoa and is able to alter the fertility potential of men by inducing the membrane impairment, changing the sperm morphology and motility, and also inducing DNA fragmentation.[22] Both chronic alcohol intake[23] and cocaine abuse[24] has been shown to impair sperm parameters. Moreover Aziz et al. demonstrated no associations between various risk factors (occupation, race, religion and smoking) and the etiologies of infertility.[10] Buiatti et al. found that azoospermia and oligozoospermia were unconcerned with coffee consumption, alcohol intake, smoking, X-ray exposure, socioeconomic status and educational level.[25]

The present study also shows that smoking does not statistically correlate with either critical spermiogram defects or abnormal physical findings. However alcohol intake seems to be related to both abnormal physical findings and serious spermatogenetic disturbances. Smoking may exert subtle effects which impair male infertility over a long period of time.

Although there are many studies in the literature that proves the almost certain relations among certain drugs, smoking, febrile or vasculitic diseases, genitourinary or surgery, abnormal physical findings and spermiogram disorders; no similar statistical correlation could be established the present study. Instead, trauma and duration of alcohol intake seem to be responsible for abnormal physical findings whereas type of infertility, duration of alcohol intake and heat exposure seem to be statistically correlated with severe sperm disorders.

Subjects diagnosed with primary infertility and abnormal physical findings had azoospermia and oligoasthenoteratozoospermia significantly more. The subjects diagnosed with primary infertility and abnormal physical findings also had significantly higher levels of gonadotropins, possibly indicating primary testicular failure.

The present study claims that the previously established, infertility-associated risk factors such as age, smoking, chronic diseases or surgery might not be as influential or might affect male infertility in more concealed aspects. Further clinical trials are required to explain the sophisticated etiopathogenesis of infertility.

Bir İnfertil Erkek Popülasyonunda Sosyodemografik Bulgular

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İnfertil erkeklerde görülen ciddi sperm üretim bozukluklarının ilişkili olduğu sosyodemografik özelliklerin belirlenmesi amaçlanmaktadır.
Androloji birimine başvuran 585 infertil erkek çalışma kapsamına alındı. Anormal fizik muayene bulgusu saptanan infertil erkeklerle fizik muayenesi normal olan infertil erkekler karşılaştırıldı. Ayrıca ciddi spermiogram bozukluğu (azospermi ve oligoastenoteratozospermi) olan infertil erkeklerle diğer spermiogram bozukluklarının belirlendiği infertil erkekler kıyaslandı.
Katılımcıların çoğu, infertiliteye neden olabilecek cerrahi girişim, kronik hastalık, travma, ilaç kullanımı veya gonadotoksin maruziyeti öyküsü olmayan primer infertil erkeklerdi. En sık saptanan fizik muayene bulgusu olan testiküler atrofi ile travma arasında anlamlı bir ilişki vardı. Ciddi spermiogram bozuklukları olarak kabul edilen azospermi ve oligoastenoteratozospermi, anormal fizik muayene bulguları ve gonadotoksin (özellikle ısı) maruziyetiyle yakından ilişkiliydi.
Literatürde yer alan benzer çalışmalarda, erkek infertilitesiyle ilişkili olduğu öne sürülen yaş, sigara tüketimi ve cerrahi gibi etkenlerin düşünüldüğü kadar etkili olmadığı veya diğer olası etmenlerle birlikte etkinlik gösterdiği öne sürülmüştür.

Anahtar Kelimeler: Azospermi, Erkek infertilitesi, Etyopatogenez, Spermiogram

References

1. Brehm R, Steger K, Regulation of Sertoli cell and germ cell differentiation, Adv Anat Embryol Cell Biol. 2005; 181:1-93.
2. Sharlip ID, Jarow JP, Belker AM et al, Best practice policies for male infertility, Fertil Steril 2002;77:873.
3. Jarow JP, Espeland MA, Lipshultz LI. Evaluation of the azoospermic patient. J Urol 2002;142:62.
4. Guzick DS, Overstreet JW, Factor-Litvak P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. New Engl J Med 2001;345:1388.
5. World Health Organization, Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction, 4th, Cambridge University Press, 1999.
6. Kidd SA, Eskenazi B, Wyrobek AJ, Effects of male age on

semen quality and fertility: a review of the literature, Fertil Steril 2001;75:237.

7. Hassan MA, Killick SR, Effect of male age on fertility: evidence for the decline in male fertility with decreasing age. Fertil Steril 2003;79 (Suppl 3):1520.
8. Merino G, Carranzo-Lira S. Semen characteristics, endocrine profiles, and testicular biopsies of infertile men of different ages. Arch Androl 2005;35:219-24.
9. Pasqualotto FF, Sobreiro BP, Hallak J, et al. Sperm concentration and normal sperm morphology decrease and follicle-stimulating hormone level increases with age. BJU Int. 2005;96:1087-91.
10. Aziz N, Agarwal A, Naillella ICP. Relationship between epidemiological features and etiology of male infertility as diagnosed by a comprehensive infertility service provider. Reprod Biomed Online 2006;12:209-14.
11. Ghazzal AM. Inguinal hernias and genital abnormalities in young Jordanian males. East Mediterr Health J. 2006;12: 483-8.
12. Sheynkin YR, Hendin BN, Schlegel PN, Goldstein M, Microsurgical repair of iatrogenic injury to the vas deferens, J Urol 1998;159:139.
13. Hayashi T. Drug-induced impaired spermatogenesis. Nippon Rinsho 2006;2:326-9.
14. Schlegel PN, Chang TSK, Marshall FF, Antibiotics: potential hazard to male fertility, Fertil Steril 1991;55:235.
15. Traina ME, Guarino M, Urbani E, et al. Long-term effects on male gonadal function of antitumoral drugs used during childhood. Minerva Pediatr 2006;58:183-91.
16. Wang C, McDonald V, Leung A et al, Effect of increased scrotal temperature on sperm production in normal men, Fertil Steril 1997;68:334.
17. Parazzini F, Marchini M, Luchini L et al, Tight underpants and trousers and risk of dyspermia, Int J Androl 1995;18: 137-40.
18. Swan SH. Semen quality in fertile US men in relation to geographical area and pesticide exposure. Int J Androl. 2006;29:62-8.
19. Toft G, Rignell-Hydborn A, Tyrkiel E, et al. Semen quality and exposure to persistent organochlorine pollutants. Epidemiology 2006;17:450-8.
20. Aitken RJ, Shakkeback NE, Roman SD. Male reproductive health and environment. Med J Aust 2006;185:414-5.
21. Lee HY. Studies on male infertility: Clinical observation on male infertility. Tachan Uihale Hyophoe Chi 1970;13: 1008-17.
22. Kunzle R, Mueller MD, Hanggi W et al, Semen quality of male smokers and nonsmokers in infertile couples, Fertil Steril 2003;79:287.
23. Vicari E, Arancio A, Giuffrida V, et al. A case of reversible azoospermia following withdrawal from from alcohol consumption. J Endocrinol Invest 2002;25:473-6.
24. Bracken MB, Eskenazi B, Sachse K et al, Association of cocaine use with sperm concentration, motility, and morphology, Fertil Steril 1990;53:315.
25. Buiatti E, Barchialli A, Geddes M, et al. Risk factors in male infertility: a case-control study. Arch Environ Health 1984;39:266-70.