Original Article

A population-based study of the epidemiology and the risk factors for male infertility in Kuwait

Ahmed M Al-Kandari[1], Ahmad N. Al-Enezi[2], Hamdy Ibrahim[3], Omar Alkandari[4]

[1]Department of Surgery (Urology), Faculty of Medicine, Kuwait University, Safat, [2]Department of Surgery, Urology Unit, Mubarak Al-Kabeer Hospital, Sabah Al-Ahmad Center, Kuwait, [4]Department of Pediatrics, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait, [3]Department of Urology, Fayyoum University, Fayyoum, Egypt

Abstract

Purpose: Infertility has become one of the foremost public health concerns, affecting a large number of couples. This research aimed to study and analyze the epidemiological data of male infertility including demographic characteristics and potential accountable factors.

Materials and Methods: A population-based study was carried out among male patients of one center. Different factors have been investigated such as family history, smoking, and varicocele. Data were analyzed using the STATA statistical software package.

Results: A total of 608 male patients aged between 22 and 56 years were included. Out of them, there were 544 (89.95%) married, 48 (7.9%) married more than once, and 10 (1.6%) divorced. Primary infertility was noted in 478 (78.6%) patients. The most commonly reported sexual disorder was erectile dysfunction 53 (8.7%), while decreased libido was detected in 8 (1.3%) patients. Varicocele was present among 507 (86%) patients. Semen analyses of infertile patients revealed that 43 (8.2%) cases had normal semen tests. In contrast, oligoasthenospermia was the most commonly reported semen abnormality 158 (30.2%). A total of 198 patients underwent assisted reproductive technique.

Conclusion: This study concluded that primary infertility is the most common type among all infertile male patients who visited our center. The risk factors of male infertility include positive family history, smoking, and varicocele.

Keywords: Male infertility, smoking, varicocele

Address for correspondence: Dr. Ahmed M Al-Kandari, Department of Surgery (Urology), Faculty of Medicine, Kuwait University, P. O. Box 24923, Safat 13110, Kuwait.
E-mail: drakandari@hotmail.com
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INTRODUCTION

Infertility is one of the major public health concerns, affecting 15% of couples seeking pregnancy. Male partners were responsible for around half of the infertility records reported.[1] Male infertility is a multifactorial condition that necessitates proper understanding and awareness of the geographic variations and associated factors, especially in relation to genetic factors. In this prospect, information about global data on infertility is worth mentioning. For instance, around 5%–6% of males are infertile in North America, 8% in Australia, and 7.5% in Europe.[2-4]

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On the contrast, the infertility rates are higher in North Africa, Sub-Saharan Africa, and Eastern Europe and Middle East countries when compared to North America, Australia, and Europe.[5] In the Middle East countries including Egypt, Qatar, and Saudi Arabia, the male infertility is towering. Of note, there are no rigorous statistics of male partner infertility rates in Northern Africa and the Middle East compared to female partner infertility. Health-care professionals believe that male infertility is underreported owing to the cultural beliefs and even patriarchal societies. It is noteworthy that males usually refuse to undergo neither the laboratory assessment procedures of infertility nor the primary clinical screening and sexual care.[6]

The epidemiology of male infertility is a critical and worth investigation and research. Screening programs and early diagnosis will undoubtedly expedite prompt and proper management. We believe that there is a lack of knowledge with regard to male infertility among the Kuwait population. Therefore, this study has been conducted to identify infertile male patients and analyze potential risk factors including family history, smoking, and varicocele.

MATERIALS AND METHODS

Study design and study population

This study is a prospective observational study that has been carried out among 608 male participants of Kuwait city from a single center. The study has been conducted in accordance to the Declaration of Helsinki, and the ethical approval was signed by the ethical committee senior staff members. All patients who visited our center (2007–2017) seeking consultation regarding male infertility were included.

Assessment procedures

All patients have received initial general clinical examination and assessment upon admission. Afterward, the varicocele assessment was performed clinically while the patient in a standing position. Then, it has been confirmed by the color Doppler ultrasound technique that revealed dilated spermatic vein over 2 mm with reflux. The subclinical varicocele is usually not palpable, so the ultrasound diagnosis of varicocele comprised patients with clinically palpable varicocele only. The color Doppler ultrasound is considered the most reliable and feasible method for diagnosing clinical and subclinical varicocele. The existence of veins larger than 2 mm in diameter is a standardized criterion for precise diagnosis.[7] Hormonal profile has been also considered including follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin, and estradiol. The chromosomal tests have been selectively performed in patients with severe oligospermia (<5 million/ml) or even azoospermia. This included chromosomal karyotype and Y chromosome microdeletion test. Patients with azoospermia underwent testicular sperm extraction (TESE). Standard TESE technique was implemented in most of the cases, while microsurgical TESE (microTESE) was followed in the remaining cases. The selection criteria to do either standard TESE or micro TESE was based on physician judgment and personal experience meaning that trained urologist in microscopic surgery will prefer and do micro TESE. This study also included a number of cases who underwent intrauterine insemination (IUI), intracytoplasmic sperm injection (ICSI), or both. Moreover, we also evaluated the assisted reproductive techniques (ART) among the included patients. Although all data have been collected and analyzed between 2007 and 2017, the reference values of semen analysis tests were interpreted according to the World Health Organization semen analysis data 5th edition-2010.[8]

Outcomes and statistics

This research aimed to evaluate the epidemiological data of male infertility. Multiple demographics and clinical factors have been investigated and analyzed including age, marital status, family history of male infertility, smoking, and being primary or secondary infertility. Family history considered to be positive when one or more brothers or uncles suffered from male infertility. The incidence of varicoceles and the incidence of sexual dysfunction including libido, erectile, and ejaculatory disorders were also considered among research objectives. In addition, we assessed the social marital status issues including married, married more than once, and divorced. Data were analyzed using the STATA statistical software package (STATA v.12, STATA Corporation, College Station, TX, USA). Continuous variables presented as median and range, whereas categorical variables expressed as number and percentage.

RESULTS

A total of 608 male patients aged between 22 and 56 years were included. Out of them, there were 544 (89.95%) married, 48 (7.9%) married more than once, and 10 (1.6%) divorced. Primary infertility was noted in 478 (78.6%) patients, while secondary infertility in residual cases. Positive family history and smoking were noticed among included patients with 13.5% and 40.8%, respectively. The baseline characteristics of the study population are shown in Table 1.

Most of the included patients, i.e., 475 (78.1%), had no sexual dysfunction problems. However, we reported

multiple dysfunction disorders among residual cases. The most commonly reported disorder was erectile dysfunction 53 (8.7%). Decreased libido was detected in 8 (1.3%) patients, while ejaculatory dysfunction was reported in 22 (3.6%) cases. There were 23 (3.8%) patients who experienced combined erectile and ejaculatory dysfunction. Furthermore, a total of 18 (3%) had combined decreased libido and erectile dysfunction. Only 5 (0.8%) reported combined decreased libido, erectile dysfunction, and ejaculatory dysfunction, whereas only 4 (0.7%) patients had combined decreased libido and ejaculatory dysfunction. Varicocele was present among 507 (86%) patients. The distribution of varicoceles is detailed in Table 2.

Semen analyses of infertile patients revealed that 43 (8.2%) cases had normal semen tests. On contrast, oligoasthenospermia was the most commonly reported semen abnormality 158 (30.2%). Nonobstructive azoospermia was detected in 115 (22%) patients, while obstructive azoospermia was reported in 2 (04%) patients only. In addition, laboratory evaluation revealed 92 (17.6%) patients with oligospermia and 114 (21.8%) with asthenospermia.

Hormonal studies of 232 patients showed that about 21.5% had high FSH, 11.69% had high LH, 9.48% had high prolactin, 3% had high estradiol level, and 15.95% had low testosterone. Other abnormal hormones data showed that 9.48% had high prolactin and 3% had high estradiol level. Only 64 patients went through chromosomal analysis procedure. Three patients had chromosomal analysis abnormality; two cases with Klinefelter syndrome (47 XXY), and one case of chromosome 3 abnormality.

A total of 198 patients underwent ART, 33 (5.4%) cases underwent IUI, 155 cases (25.5%) underwent ICSI, and 10 (1.7%) cases received both IUI and ICSI. Of the 198 patients with ART, only 164 patients were followed up, in which pregnancy occurred in 43 (26.2%) patients. Patients with nonobstructive azoospermia were treated with TESE: ten cases of as microTESE and the remaining cases through standard TESE.

Table 1: Baseline demographics and clinical characteristics of the study population

Variable	*n* (%) or median (range)
Age	31 (22-56)
Marital status	
Single	6 (1)
Married	544 (89.5)
Divorced	10 (1.6)
>1 married	48 (7.9)
Positive family history of infertility	82 (13.5)
Smoking	
No	297 (42.8)
Yes	248 (40.8)
Ex-smoking	63 (10.4)
Infertility type	
Primary	478 (78.6)
Secondary	130 (21.4)

Table 2: Number of varicocele among patients with infertility

Etiology	*n* (%)
No varicocele	82 (14)
Varicocele	507 (86)
Left	254 (43)
Right	5 (0.9)
Bilateral	248 (42.1)

DISCUSSION

The prospective study included a total of 608 male patients of different demographics. The prevalence of primary male infertility was remarkable (78.6%), which is inconsistent with a previously published study of 289 patients, whereas only 10.4% of the patients had primary male infertility due to either chromosomal anomalies or Y chromosome microdeletions.[9] In our study, a positive family history of male infertility was noted in 13.5% of included patients, which attest the role of genetic factors in inducing male infertility. Although the chromosomal analysis test is efficient in the diagnosis of genetic disorders related to male infertility, it was not frequently performed in this study because of cost issues. Moreover, there are multiple potentially genetic factors of male infertility, which are difficult to identify.[10]

Smoking is an influential risk factor of male infertility and has been reported in 51.2% of the patients included in our study.[11] Smoking releases cadmium (Cd) that causes an imbalance in the level of reactive oxygen species of seminal plasma, which, in turn, procure DNA damage.[12] In addition, smoking also reduces the sperm motility and percentage of normal sperm cells.[13] Therefore, health-care professionals should recommend smoking cessation in the management of male infertility.

Varicocele is a common predisposing factor to male infertility since it causes impairment of testicular function and infertility. This has been proven through multiple clinical trials that showed the effects of varicocelectomy in improving semen parameters.[14] For instance, Baazeem *et al*.[15] concluded that varicocelectomy is associated with a significant rising of sperm concentration as well as total and progressive motility. Furthermore, experimental research revealed that varicocelectomy reduces seminal oxidative stress and sperm DNA damage as well as improving sperm ultramorphology.[16] Another study

conducted by Gomaa *et al*.[17] deduced that varicocele is associated with diminishing of total testosterone and T:E ratio, which were markedly improved following subsequent subinguinal varicocelectomy.[15] Clinical research also revealed improved semen parameters, DNA integrity, and assisted reproductive technology outcomes after varicocele repair (Punab *et al*.).[18] According to our results, 86% of the patients had varicocele: 43% as left-sided varicocele and 42.1% as bilateral varicoceles. On another study conducted by ElBardisi *et al*.,[14] around 37.6% had left-sided varicocele while only 5.5% had bilateral varicocele.[17]

In the present study, semen abnormalities among our patients revealed that 91.8% of the cases had abnormal semen tests such as oligoasthenospermia. The nonobstructive azoospermia was more common than obstructive azoospermia; this may be due to vasectomy being uncommon in Kuwait and the most common cause for obstructive azoospermia. On the other hand, many factors adversely affect sperm quality, including varicocele, accessory gland infection, immunological factors, congenital abnormalities, and iatrogenic systemic and endocrine causes such as diabetes mellitus, obesity, metabolic syndrome, and smoking.[19] These data highlight an obvious gap and shortage of knowledge regarding the causes, biological mechanisms, and pathways behind impaired spermatogenesis and male reproductive physiology.[20]

Our results revealed that only 21.5% had high FSH, 11.69% had high LH, and 15.95% had low testosterone. Fertility in men requires normal functioning of the hypothalamus, pituitary glands, and testes. The male germ cell development is dependent on the balanced endocrine secretion of these glands.[21]

In about 40% of primary testicular failure, the etiology remains unknown; however, anonymous genetic anomalies may be involved in some cases. Laboratory biological research presented a leading role in exploring possible gene interactions and common biological pathways. Although these novel approaches will certainly assist in better understanding of genetic factors, a real perception of the etiopathogenesis of idiopathic male infertility will only be achieved through parallel investigation of the gene-environmental interaction and epigenetics.[22]

A study conducted by Eldamnhoury *et al*.[23] found that leukocytospermia is associated with reduction in sperm count, progressive motility, and further upregulation of seminal interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). In addition, all patients were assessed by detailed fertility history as well as entire medical and sexual examinations. Laboratory assessment included hormonal and semen analysis and assessment of IL-6 and TNF-α in semen plasma. There were significant differences among study arms in terms of total sperm count, sperm concentration, and progressive motility ($P < 0.05$ for each).[23] In our study, only 64 patients underwent chromosomal analysis and only 3 cases had chromosomal analysis abnormality. In another study, chromosomal abnormalities were detected in 12 patients.[24]

According to a study carried out, the assessment of sperm DNA fragmentation (SDF) testing may be a crucial prognostic value for assessment and diagnosis of male infertility factors.[25] The authors have performed several conventional assessments of semen and looked for female infertility ahead of assessment of SDF. The sources of sperm with SDF include nuclear remodeling disorders with spermatogenesis and other posttesticular factors. These disorders result in rising of oxidative stress, which ultimately give rise to damage of the sperm DNA integrity. A value above 25% of the SDF index indicates a higher chance of miscarriage and pregnancy failure or longer duration until achieving pregnancy.[26]

If the primary assessment indicated correctible etiology such as varicocele or leukocytospermia, proper interventions for these conditions should be offered such as varicocelectomy or antibiotic therapy. For the cases with idiopathic infertility, the increased levels of SDF may rationalize empirical remedies such as antioxidant therapy or lifestyle modifications including cessation of cigarette smoking.[27] It has been noted that researchers utilize the testicular sperm rather than ejaculated sperm in men with high SDF, oligozoospermia, or recurrent IVF failure.[28,29]

Limitations and recommendations

Our study included a large sample population; however, it has several limitations. Chromosomal analysis and hormonal studies have not performed for all included participants. Another limitation is that our study lacks for random sampling and controlled arm. It also has been conducted at one center which may manipulate the results. Future large-scale randomized studies are needed to extensively investigate male infertility. Primary health-care programs for screening and treatment of male infertility can improve the patients' quality of life.[21] Standardized measures should be designed to identify sexual disorders in infertile couples, and health-care professionals should be trained in order to efficiently manage and propose strategies to overcome sexual disturbances. This approach could

preserve the overall quality of life including sexual life as well as the enhancing pregnancy opportunities in ART.[30]

CONCLUSION

To recapitulate, this population-based epidemiological study concluded that primary infertility is the most common type among all infertile male patients who visited our center. The risk factors of male infertility include positive family history, smoking, and varicocele. Sexual dysfunction is an important consequence and worth clinical attention and investigation. Future multicenter random controlled studies are recommended to build conclusive evidence and improve the overall quality of life as well as sexual practice.

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Conflicts of interest
There are no conflicts of interest.

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