Original Article

Clinical, endocrinological and histopathological patterns of infertile Saudi men subjected to testicular biopsy: A retrospective study from a single center

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Abstract

Purpose: To evaluate the outcome of testicular biopsies as well as the etiology of azoospermia and severe oligospermia in Saudi men referred for tertiary care. To correlate testicular histology with patients' clinical and hormonal profiles.

Materials and Methods: Charts of men subjected to testicular biopsies in the last 10-year period were retrospectively reviewed. Relative history and physical examination findings were reported. Results of male fertility profile tests and semen analysis of at least two ejaculates were collected. Reported histopathology was obtained.

Results: Reports of 229 patients were included; 199 (86.9%) with azoospermia and 30 (13.1%) with severe oligospermia. The mean (SD) age was 30.6 (6.4) years. A small right or left testis was reported in 88 (38.4%) and 87 (38%) of the patients, respectively. The mean (SD) testosterone and follicle stimulating hormone (FSH) values were 17.2 (7.2) nmol/L and 13.1 (10.9) IU/L, respectively. Hypospermatogenesis was the most common histology encountered (36.5%), followed by Sertoli cell-only (SCO) histology (31.5%). Low testicular volume ($P = 0.000$), high FSH ($P = 0.001$) and high leutenizing hormone (LH) ($P = 0.001$) were found to be of significantly adverse effect on spermatogenesis. Despite having bilateral small testes, high serum FSH and LH, 24.3% of our patients showed active spermatogenesis.

Conclusions: Hypospermatogenesis was the most common pattern of spermatogenic defect in our patients. SCO histology was the most common pattern in patients with small testes, primary testicular failure, primary infertility and azoospermia. Low testicular volume, high FSH and LH are significantly associated with impaired spermatogenesis. Even with severe male factor infertility disorders, infertile men can have some spermatogenesis.

Key Words: Hormone profile, male infertility, spermatogenesis, testicular biopsy

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INTRODUCTION

Infertility is the inability to conceive after 1 year of regular unprotected intercourse.[1,2] Male factor is a major cause of infertility among couples, contributing to more than half of all cases of infertility.[3,4]

The incidence of male infertility and the subsequent

histological findings in testicular biopsies differ significantly from one part of the world to another due to several underlying etiological factors, including social habits, genetic causes and environmental conditions such as underlying infections, chemicals, radiation and exposure to heat.[5]

Evaluation of male infertility includes a thorough clinical history taking, physical examination, semen analysis, hormonal assay and search for antisperm antibodies. Transrectal ultrasonography, vasography and testicular biopsy are additional tests.[6] The latter is particularly useful in cases of azoospermia or severe oligospermia with normal endocrine function.[7,8] Azoospermia is present in about 1% of all men and in approximately 15% of infertile men.[9,10]

In this study, the different clinical, etiological and endocrinological profiles of infertile azoospermic or severe oligospermic Saudi men, from the central region, subjected for testicular biopsies in our center, were reviewed. The testicular histopathological patterns of those patients were determined. Correlations among hormonal profile, clinical characteristics and testicular histology were evaluated.

MATERIALS AND METHODS

After the hospital ethics committee approval, records of infertile, non-vasectomized azoospermic or severely oligospermic men subjected for unilateral or bilateral diagnostic testicular biopsies in the last 10-year period were retrospectively reviewed. Presence of azoospermia was documented in at least two semen specimens, all processed with centrifugation at 3000 g for 15 min, and extensive examination of the resuspended pellet.[11] Severe oligospermia was defined as the presence of less than 5 million sperms in the ejaculate.

History of cryptorchidism, genital infections, trauma and scrotal and pelvic surgeries were reported. Findings of external genitalia examination for number, size, consistency and location of the testes as well as the epididymides and the scrotal part of the vasa deferentia were obtained. Testicular size was measured with an orchidometer or ultrasonography in testes smaller than 8 ml. According to the size, each testis was categorized into small (less than 15 ml) or average sized (15 ml or greater).

Results of male fertility profile tests were collected. Blood samples were obtained at 09:00 and centrifuged for 20 min. The serum was separated and either examined immediately or stored at -20°C until analysis was performed. The serum levels of follicle stimulating hormone (FSH), leutenizing hormone (LH), testosterone and prolactin were measured by the immunochemiluminescent method.

Testicular biopsies were performed according to the technique published by Silber *et al*.[12] under general, epidural or subcutaneous anesthesia with cord block. After stabilization of the testicle, a small incision in the testicle's mid portion was performed, cutting through the scrotal skin, tunica vaginalis and tunica albuginea. A substantial piece of the extruding testicular tissue was cut with small scissors and sent in Bouin's solution for histological evaluation.

All testicular biopsies were processed as routine, stained with hematoxylin and eosin (H and E) and examined histologically by light microscopy. Men were categorized according to McLachlan and associates[13] as having normal spermatogenesis (full spermatogenesis in the entire biopsy with normal intertubular tissue), hypospermatogenesis (an equivalent reduction in numbers of spermatogonia and primary spermatids), diffuse tubular atrophy with tubular hyalinization or sclerosis (no germ cell or Sertoli cell present in the tubules with peritubular fibrosis), maturation arrest (block in the maturation to spermatids at either the primary spermatocyte or spermatogonia stage with total absence of the later stages of spermatogenesis) or Sertoli cell-only (SCO) syndrome (the absence of germ cells in the seminiferous tubules) based on the most advanced pattern of spermatogenesis on histological examination.

Descriptive statistics are presented as the mean ± SD and percent. The chi-square test was used to evaluate the association among different variables. A *P*-value of less than 0.05 was considered significant for all tests performed. For the purpose of studying their effect as predictors of spermatogenesis (presence of histological evidence in testicular biopsy), values of FSH and LH were further categorized into normal or high. Factors proven to be of significant adverse effect on spermatogenesis (adverse predictive factors) were combined to test the effect of their combination on the process of spermatogenesis.

RESULTS

Reports of 229 patients were included. The mean (SD) age was 30.6 (6.4) years. Presentations were primary infertility in 184 (80.3%) patients for a mean of 4.9 ± 4.3 years and secondary infertility in 32 (14%) for a mean of 7.3 ± 4.4 years. Premarital examination and work-up for hypogonadism or varicocele was the presentation in 13 (5.7%) patients. History of mumps orchitis was encountered in five patients, cryptorchidism in five, vasoepididymostomy in two, left testicular torsion in one, left orchidectomy in three and bilateral inguinal herniorrhaphy in four.

All patients, but two, showed good secondary sex characters. A small right or left testis was reported in 88 (38.4%) and

87 (38%) of the patients, respectively. Of the patients, 136 (59.4%) had bilateral average testes, 11 (4.8%) had unilateral small testes and 82 ((35.8%) showed bilateral small testes. Left varicocele was diagnosed in 42 (18.3%) patients while 19 (8.3%) had bilateral varicocele. No relevant history or physical examination abnormality could be documented in 76 (33.2%) patients.

Azoospermia was diagnosed in 199 (86.9%) and severe oligospermia in 30 (13.1%) of the biopsied men. The mean (SD) testosterone, FSH and LH values were 17.2 (7.2) nmol/L, 13.1 (10.9) IU/L and 8.4 (6.4) IU/L, respectively. Hyperprolactinaemia more than two-folds was encountered in five patients (2.2%). Primary testicular failure was evident in 45 patients (19.7%). No cases of secondary testicular failure were encountered.

Eleven patients (4.8%) had unilateral and 218 (95.2%) had bilateral testicular biopsies, with a total of 447 biopsied testes. Hypospermatogenesis was the most common histological pattern encountered (36.5%), followed by SCO histology (31.5%), as shown in Table 1. Right and left testicular biopsies showed different histopathological patterns in 17 patients at a histology discordance rate of 7.8%. No cases of carcinoma *in situ*, chronic granuloma or orchitis were identified in the study population.

Hypospermatogenesis was the most prevalent pattern (62.1%) in patients with oligospermia. It was also the most common pattern in secondary infertility patients, accounting for up to 51.6%, and the second most common (34.5%) in those with primary infertility. SCO was the most common histopathology pattern encountered in patients with azoospermia and in those with primary infertility, accounting for 34.7% and 35.1%, respectively [Table 2]. Of 175 small testes, 169 were biopsied, and SCO histopathology was the most common pattern [Table 2]. Primary testicular failure (high FSH, LH and low testicular volume) was diagnosed in 45 patients in whom 85 testes were biopsied. SCO and diffuse tubular atrophy were the most common histopathology patterns encountered in this group, accounting for 38.8% and 31.8%, respectively [Table 2].

The association among spermatogenesis and different clinical (secondary sex characters, testicular size, associated varicocele) and hormonal profile is shown in Table 3. Low testicular volume ($P = 0.000$), high FSH ($P = 0.001$) and high LH ($P = 0.001$) were found to be of significantly adverse effect on spermatogenesis. Increasing the number of multiple adverse predictors in a patient significantly ($P = 0.000$) decreases his chance of spermatogenesis [Table 4]. Despite having bilateral small testes, high serum FSH and LH, 24.3% of our patients showed active spermatogenesis [Table 4].

Table 1: Histopathological patterns of testicular biopsy in the study population

Pattern	Right testis (%)	Left testis (%)	Total (%)
Normal spermatogenesis	13 (5.9)	13 (5.8)	26 (5.8)
Hypospermatogenesis	80 (36)	83 (36.9)	163 (36.5)
Sertoli cell only	69 (31.1)	72 (32)	141 (31.5)
Maturation arrest	31 (13.9)	30 (13.3)	61 (13.7)
Diffuse tubular atrophy	23 (10.4)	24 (10.7)	47 (10.5)
Nonrepresentative tissue	6 (2.7)	3 (1.3)	9 (2)
Total	222 (100)	225 (100)	447 (100)

DISCUSSION

Reduced male fertility can be the result of congenital and acquired urogenital abnormalities, infections of the genital tract, increased scrotal temperature (varicocele), endocrine disturbances, genetic abnormalities and immunological factors. No causal factor, i.e. idiopathic male infertility, is found in 60–75% of the cases.[14] Idiopathic male infertility comprised 33.2% of our patients. Obviously, our study cohort is a group of azoospermic and severely oligospermic men with severe male factor infertility disorder. Furthermore, up to 27% had varicocele and about 41% had small uni- or bilateral testes.

The longer a couple has to try to conceive, the smaller the chance of spontaneous conception. If the duration of subfertility is less than 3 years, a couple is 1.7-times more likely to conceive than couples who have been trying for longer. With unexplained subfertility of more than 3 years, the chances of conception occurring are about 1–3% each cycle.[15] The mean (SD) duration of primary and secondary infertility in our patients was 4.9 (4.3) and 7.3 (4.4) years, respectively. Again, this could be attributed to the marked impairment of fertility in

Table 2: Distribution of testicular histopathology patterns in different patients' conditions

Pattern	Small testes (%)	Primary testicular failure patients (%)	Primary infertility patients (%)	Secondary infertility patients (%)	Oligospermia patients (%)	Azoospermia patients (%)
Normal spermatogenesis	3 (1.8)	1 (1.2)	18 (5)	7 (11.3)	7 (12.1)	18 (4.6)
Hypospermatogenesis	39 (23.1)	15 (17.6)	124 (34.5)	32 (51.6)	36 (62.1)	131 (33.7)
Sertoli cell only	74 (43.8)	33 (38.8)	126 (35.1)	3 (4.8)	6 (10.3)	135 (34.7)
Maturation arrest	11 (6.5)	3 (3.5)	49 (13.7)	8 (12.9)	8 (13.8)	51 (13.1)
Tubular atrophy	35 (20.7)	27 (31.8)	35 (9.8)	11 (17.8)	0 (0)	46 (11.8)
Nonrepresentative tissue	7 (4.1)	6 (7.1)	7 (1.9)	1 (1.6)	1 (1.7)	8 (2.1)
Total	169 (100)	85 (100)	359 (100)	62 (100)	58 (100)	389 (100)

Table 3: Impact of different variables on spermatogenesis

Variable	Spermatogenesis	No spermatogenesis	*P*
Secondary sex characters			0.498
Good	113 (50)	113 (50)	
Poor	0 (0)	2 (100)	
Right testicular volume			0.000
Average	85 (60.3)	56 (39.7)	
Small	28 (32.2)	59 (67.8)	
Left testicular volume			0.000
Average	82 (59)	57 (41)	
Small	39 (33.7)	57 (66.3)	
Varicocele			0.481
Left	24 (57.1)	18 (42.9)	
Bilateral	8 (42.1)	11 (57.9)	
No varicocele	82 (49.1)	85 (50.9)	
LH (IU/L)			0.001
Normal	86 (58.1)	62 (41.9)	
High	25 (34.7)	47 (65.3)	
FSH (IU/L)			0.001
Normal	82 (59.4)	56 (40.6)	
High	29 (35.4)	53 (64.6)	
Testosterone (nmol/L)			0.069
Normal	100 (50.5)	98 (49.5)	
Low	1 (12.5)	7 (87.5)	
High	7 (63.6)	4 (36.4)	
Prolactin			0.428
Normal	96 (51.3)	91 (48.7)	
High	14 (43.8)	18 (56.2)	

Figures in parenthesis are in percentage

Table 4: Impact of combined adverse predictors on spermatogenesis

Adverse predictors	Spermatogenesis	No spermatogenesis	*P*
No adverse predictors	65 (64.4)	36 (35.6)	0.000
Less than 4 predictors	39 (43.3)	51 (56.7)	
4 adverse predictors	9 (24.3)	28 (75.7)	

Figures in parenthesis are in percentage

our patients, with markedly reduced likelihood of spontaneous conception and failed previous expectant management.

Testicular biopsy is the only parameter for determining testicular histopathology pattern.[16] It remains a key investigation for distinction of defective spermatogenesis from genital tract obstruction, particularly in patients with normal FSH and testicular volume.[7,8] The distinction between obstructive and nonobstructive causes is important as men with obstructive etiologies may have other cost-effective treatment options, such as microsurgical reconstruction of the reproductive tract.[8] Furthermore, testicular biopsy is important in the evaluation of men at risk for carcinoma *in situ* or testicular cancer, such as those with idiopathic infertility, prior cryptorchidism, history of testicular neoplasia or the presence of suspicious clinical or radiological findings such as a nodule or microlithiasis.[13] Testicular biopsy can also be performed as part of a therapeutic process in patients with clinical evidence of nonobstructive azoospermia who decide to undergo intracytoplasmic sperm injection (ICSI).[8]

In our study, normal spermatogenesis was reported at a low frequency of 5.6%, suggesting possible posttesticular obstructive etiologies. Meinhard *et al*.[17] reported a similar incidence of 5%. An incidence of 11–16% has been reported.[18,19]

Hypospermatogenesis was the most common histopathological pattern encountered in our study (36.5%). Locally, an incidence of 25–29% was reported in the Western part of Saudi Arabia.[18,20] Al-Rayess and Al-Rikabi[21] from Riyadh showed an incidence of 13%. Variable results have also been reported ranging from 23% to 55.8%.[17,19]

SCO was the second most common histopathological pattern in the present study (31.5%). This finding correlates well with other studies from Saudi Arabia.[18,21,22] SCO syndrome is an irreversible change that can be associated with many underlying conditions including cryptorchid testis, orchitis, postradiation or chemotherapy, estrogen or androgen therapy and as a consequence of chronic hepatopathology.[23] Similarly, in our study, SCO syndrome was more common in patients with small testes, primary infertility, primary testicular failure and azoospermia.

Maturation arrest was encountered in 13.7% of our patients. The incidence is similar to that reported in several local studies.[18,21,22] Others reported a lower incidence of 7%.[20]

We reported a 10.5% incidence of diffuse tubular atrophy with tubular hyalinization or sclerosis. Similar results have been reported locally.[18,21,22] Jamal and Mansoor[20] reported a higher incidence of 24%. Our results showed a high incidence of tubular atrophy in patients with primary testicular failure (31.8%) and in those with history of mumps orchitis (40%).

Comparing the results of different studies is obviously difficult. Discrepancy between different studies can be explained by the different criteria of enrolling patients for biopsy as oligospermia versus azoospermia patients, primary versus secondary infertility patients as well as percentage of those with small testes or history of mumps orchitis. Social habits, genetic causes and environmental conditions also play a role.[5,13]

Seventeen discordant cases (7.8%) with different patterns identified in right and left testes were found. McLashlan and his associates[13] in a study of 534 men referred for bilateral testicular biopsies demonstrated the relative rarity of pure phenotypes, supporting the significance of bilateral testicular biopsies for comprehensive evaluation of male infertility. Additionally, there is a significant therapeutic benefit in performing bilateral testicular biopsies when considering ICSI in the management of male infertility. Absence of sperms in one testis does not rule out their presence in the other.[8]

Generally, the levels of FSH are mainly correlated with the number of spermatogonia. FSH is often but not always elevated in patients with abnormal spermatogenesis.[24] When the number of spermatogonia is normal but there is complete spermatocyte or spermatid blockage, FSH values are within the normal range. Therefore, an elevated serum FSH is indicative of a significant problem with spermatogenesis, whereas a normal serum FSH does not guarantee intact spermatogenesis.[25,26] Patients with complete testicular failure have inadequate Leydig and Sertoli cell function that results in elevated gonadotropin levels associated with normal or low testosterone levels.

An evidence of spermatogenesis in testicular biopsy of 35.4% of our patients with elevated serum FSH demonstrated the relatively poor correlation of elevated serum FSH with absence of sperm in the testis biopsy specimen. Furthermore, evidence of spermatogenesis in 24.3% of the patients with all the adversely predictive factors indicates clearly that men with even the most severe male factor infertility disorders are potentially capable of fathering children with ICSI, and no patient with azoospermia should be excluded from testicular biopsy solely on the basis of elevated FSH and testicular atrophy.

Inhibin B is a glycoprotein hormone secreted primarily by Sertoli cells. Although the clinical use of inhibin B as a predictor of spermatogenesis is controversial,[27] the study is still limited by the lack of its use and the lack of genetic examination of the involved patients.

CONCLUSIONS

This study outlines the different patterns of testicular biopsy in male infertility encountered in our region. Hypospermatogenesis was the most common pattern of spermatogenic defect in our patients. SCO histology was the most common pattern in patients with small testes, primary testicular failure, primary infertility and azoospermia. Our results showed a 7.8% histology discordance rate between both testes. Low testicular volume, high FSH and LH are significantly associated with impaired spermatogenesis. Even with severe male factor infertility disorders, infertile men can have some spermatogenesis.

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