TESTICULAR BIOPSY AND SCROTAL EXPLORATION IN THE MANAGEMENT OF MALE INFERTILITY

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ABSTRACT

Testicular biopsy findings in 52 subfertile men were correlated with the clinical findings, semen analyses and hormonal levels. Mild to moderate pathological changes were seen in 2/3 of cases while 1/3 had severe damage. Almost 3/4 of them had atrophic testicles while up to 1/2 had varicoceles. In most cases, routine examination, semen analyses and hormonal studies could not provide an accurate guide to the severity of the lesions. Size alone correlated well with worse changes in the smaller testes. Biopsy was more precise for assessing oligospermia and azoospermia in which the histology can vary considerably. The pattern with varicocele was not pathnognonomic but maturation arrest was common in younger patients while older men tend to have sclerosis and intraluminal sloughing irrespective of the grade of venous reflux.

FSH and LH levels were only useful when either or both were raised more than 3 times. Normal FSH could be found in germinal aplasia or maturation arrest. In the latter, the testes were often of good size; thus diagnosis would not be made without biopsy. Examination of the testes, epididymis and the vasa was always done at the time of biopsy and when indicated, vasography helped elucidate the nature and site of the obstruction causing azoospermia. When a varicocele was present, biopsy of the testes at the time of ligation can provide assessment of the pathological change and provide a prognosis especially when additional hormonal treatment was being considered. The greatest value of biopsy was in cases confirmed beyond salvage by histology. This enabled appropriate action to be taken ie. AID or adoption, etc.

Keywords: *Testis, biopsy, male infertility, scrotal exploration, varicocele.*

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INTRODUCTION

Testicular biopsy in infertile men was first advocated in 1940 by Charny to distinguish cases of obstructive aspermia from non-obstructive, to classify cases of oligospermia and to aid in prognosis[1]. Its use as a diagnostic procedure has not been universally accepted. Scott in 1968 recommended it only in cases of aspermia[2] while Garduno and Mehan (1970) have used it in a wider context[3]. Meihard et al (1973) advocated testicular biopsy in infertile men for the complete assessment of the case and for identifying those which were potentially treatable[4]. They found that clinical examination and semen analysis were no guide to the severity of the lesion. The aim of this study was to re-evaluate the value of clinical findings and semen analyses and also to assess the value of hormonal investigations vis-a-vis testicular biopsy in the assessment of male infertility patients.

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METHOD

Fifty-two consecutive male patients referred for infertility to the Department of Surgery, Toa Payoh Hospital, from August 1988 to August 1989 had bilateral testicular biopsies done in addition to the usual workup (vide infra) and constitute the material for this clinical study.

All the patients were in good general health. A past history of maldescended testis, venereal disease, mumps and other causes of orchitis were sought and details of past and current medical problems and medications were recorded. Clinical examination (including assessment of the vasa and testicular size by the Prader Orchidometer and the presence of varicocele confirmed by doppler ultrasound) were done by the same examiner for all the patients. Biopsy specimens were taken under general anaesthesia through a small midline incision in the scrotum, deepened into each of the visceral tunica albuginea. The protruding tubules were amputated with dissecting scissors and sent for histology. Patients with varicocele had at the same time ligation of the varicocele. Patency of the vas deferens was tested in some of the patients by contrast vasography or methylene blue "dye" vasography when this was indicated.

RESULTS

1. Patient Profile

Out of the 52 patients, 47 (90.4%) were referred for primary subfertility while the remaining 5 (9.6%) had secondary subfertility. The mean age was 35.0 years (SD $\pm$ 4.9 years). The oldest was 50 years of age and the youngest 25. Chinese patients comprised 76.9%, Malay 18.5%, Indian 7.7% and other races 1.9%. The racial distribution was similar to the national population statistics.

2. Testicular Size

More than half of the patients had a testicular size of 10 ml or less. The distribution among the cases is displayed in Fig 1.

Fig 1. – Testicular Size (in mls) (N = 104)

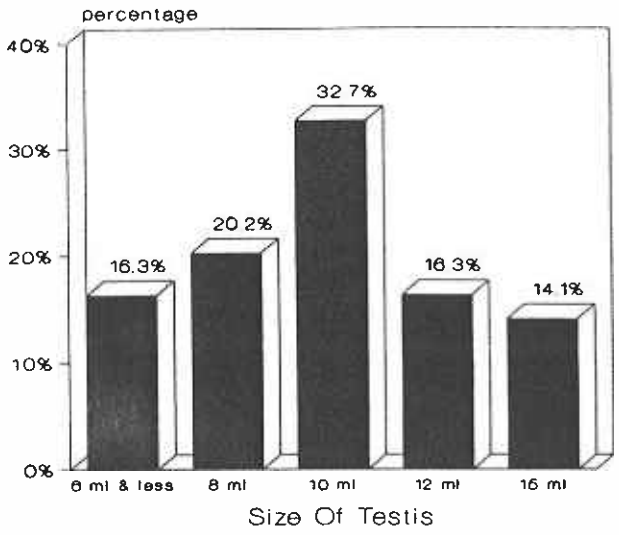
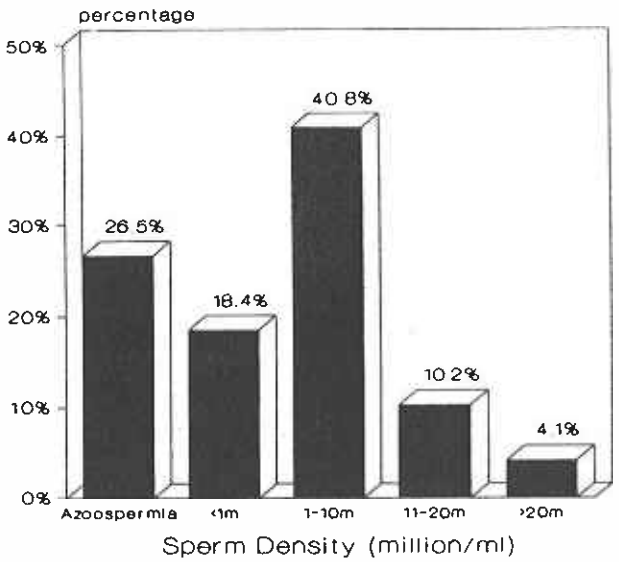


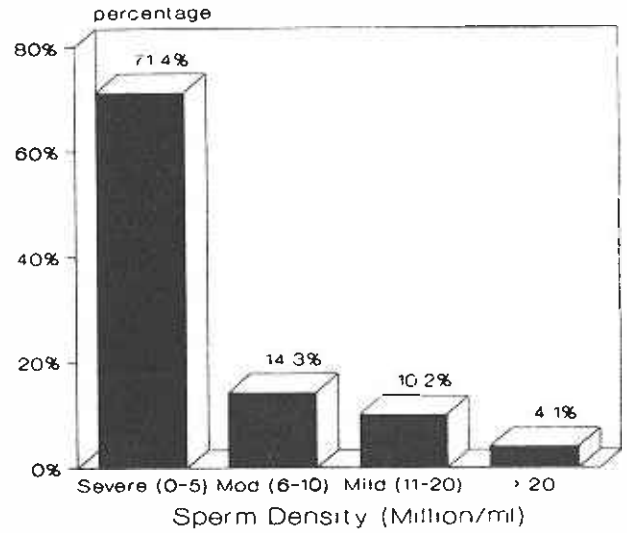
Fig 2b. – Semen Analysis (N = 49)



3. Semen Analyses

Thirty five patients (71.4%) out of 49 had severe oligospermia (0 - 5 million per ml). Thirteen patients (26.5%) out of 49 had azoospermia while another 9 (18.4%) had a sperm density of 1 million per ml or less. This is shown in Fig 2a and 2b.

Fig 2a. – Semen Analysis (Spark's Classification, 1988) (N = 49)



4. Possible Aetiological Factors

Varicoceles: Twenty-five patients (48.1%) out of 52 had varicoceles. Eighteen (34.6%) were on the left, 2 (3.8%) on the right and 5 (9.6%) had them it on both sides. For the 5 patients with bilateral varicoceles, the left was always more severe than the right side. Four patients (7.7%) had past history of varicocele with operation done. One (1.9%) patient had hernia repair, 8 (15.3%) had past history of mumps with another (1.9%) having definite previous mumps orchitis.

Vas Deferens: One patient had bilateral absence of vasa while another had unilateral absence. Cases of absence of vas were detected during clinical examination and confirmed during operation. Two patients had blockage of the right vas detected by operative vasography.

5. Hormonal Investigations

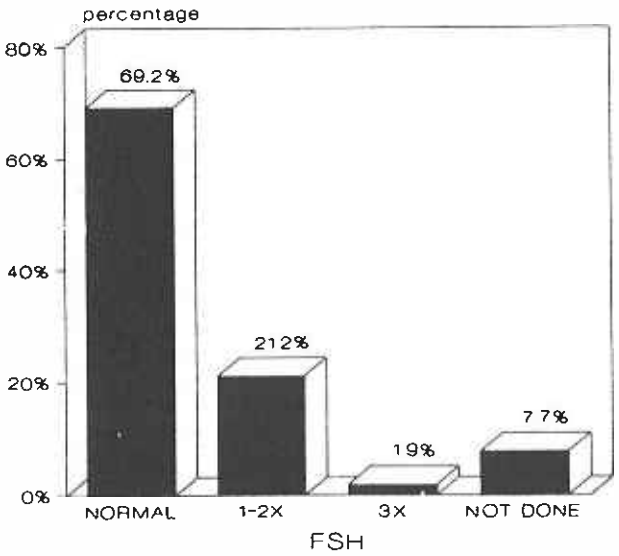
FSH Levels (Fig 3): Thirty-six patients (69.2%) had normal serum FSH while 11 (21.2%) had raised FSH levels up to 2 times normal. One patient (1.9%) had FSH levels more than 3 times normal. The FSH was not done for 4 patients (7.7%).

LH Levels (Fig 4): Fifteen (28.8%) patients had normal LH levels while 28 (53.8%) had raised levels up to 2 times normal. Two had values exceeding 3 times normal (3.8%). LH levels were not done for 7 patients (13.5%).

Testosterone Levels: Serum testosterone was normal for 39 of the 40 patients were this was done. In only one case was it slightly raised.

Prolactin Levels: Serum prolactin was done for 12 patients and all of these were in the normal range.

Fig 3. – FSH Levels (N = 52)



6. Histological Findings

The biopsy specimens were examined and classified according to the histology (Fig 5). Mild and moderate hypospermatogenesis constituted about 47.1% (49 testicles) while severe hypospermatogenesis and germinal aplasia (Sertoli-cell only histology) constituted 16.4% (17 testicles). Maturation arrest was found in 12.5% (13 testicles). Sclerosis and intraluminal

sloughing together constituted 20.2% (21 testicles). There were 4 (3.8%) testicles with normal microscopic histology.

The histology of both testicles of the same patient were identical in about 84.6% of the cases (44 pairs) and nearly so in about 9.6% of the cases (5 pairs). Only 5.8% of the patients (3 pairs) had testicles of different histology. Of the 5 pairs with very close histology, 4 pairs were of mild and moderate hypospermatogenesis while one pair was of severe hypospermatogenesis and germinal aplasia. Of the 3 pairs with different histology, one pair had mild and severe hypospermatogenesis, another pair had moderate and severe hypospermatogenesis and the last pair had maturation arrest and germinal aplasia.

Fig 4. – LH Levels (N = 52)

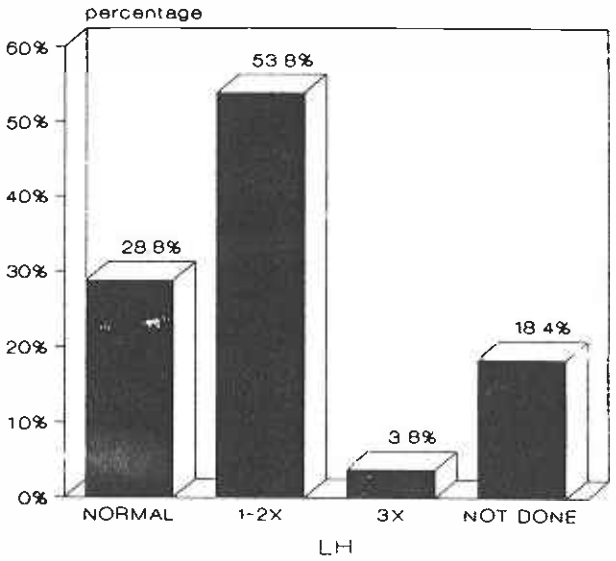
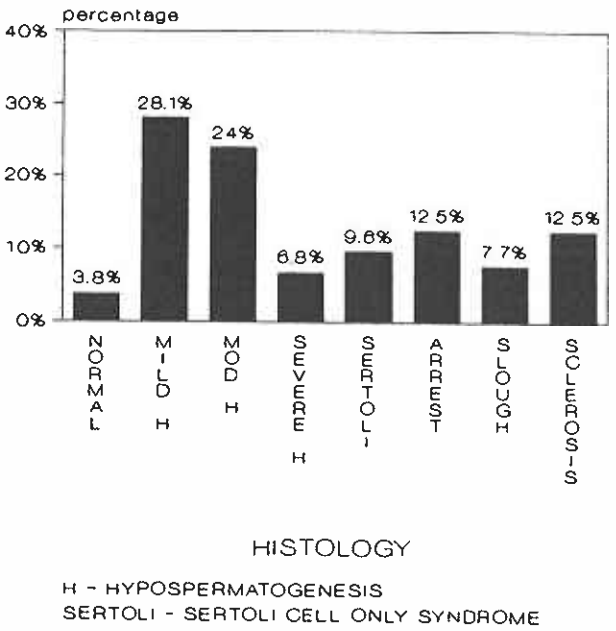


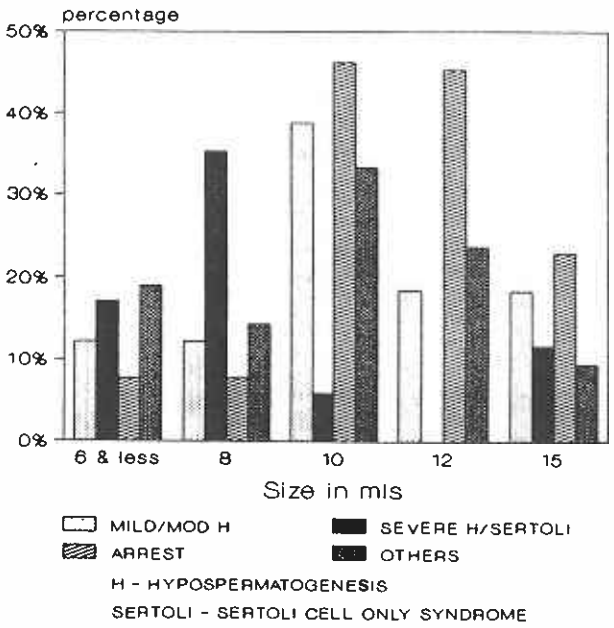
Fig 5. – Histopathology (N = 104)



7. Correlations

Histology and Testicular Size (Fig 6): There was fair correlation between testicular size and severity of the lesion. Mild and moderate hypospermatogenesis are generally associated with normal or slightly less than normal testicular size while severe hypospermatogenesis and germ cell aplasia were found in the smaller testicles. However, some normal-sized testicles were found to have severe histology or maturation arrest.

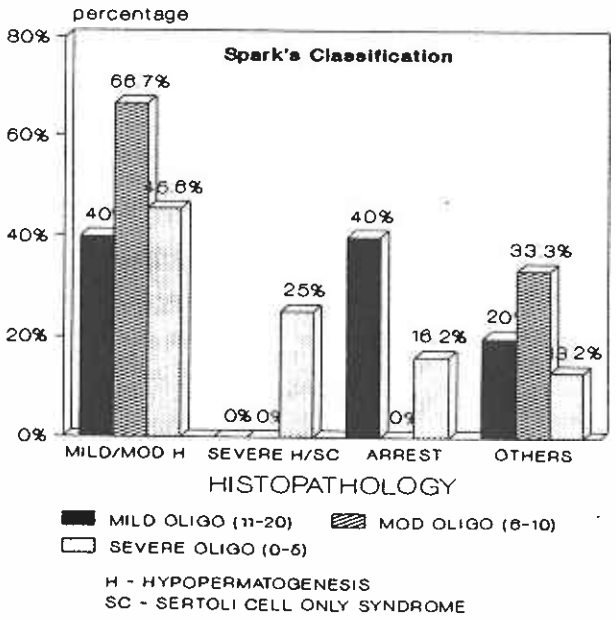
Fig 6. – Size-Histo Correlation (N = 100)



Histology and Sperm Density (Fig 7a and 7b): All histological types were seen with azoospermia and severe oligospermia. Those with higher densities ie. those with 1 million/ml or greater tend to have less severe changes.

Histology & FSH and LH (Fig 8 and 9): A markedly raised FSH and LH (if more than 3 times normal) indicated severe damage. For values lower than this the correlation was fairly poor. Normal FSH and FSH raised up to 2 times were found in all histopathological categories.

Fig 7a. – Density-Histo Correlation (N = 90)



Varicocele and Histology (Fig 10): The histopathological pattern seen in the subfertile men with varicocele is not pathognomonic. There was however a suggestion that maturation arrest was common in younger patients while older men tend to have sclerosis and sloughing.

Varicocele Side and Histology: The histopathological patterns of the ipsilateral and contralateral testes of patients with a single sided varicocele were almost identical. This seemed to

Fig 7b. – Density-Histo Correlation (N = 90)

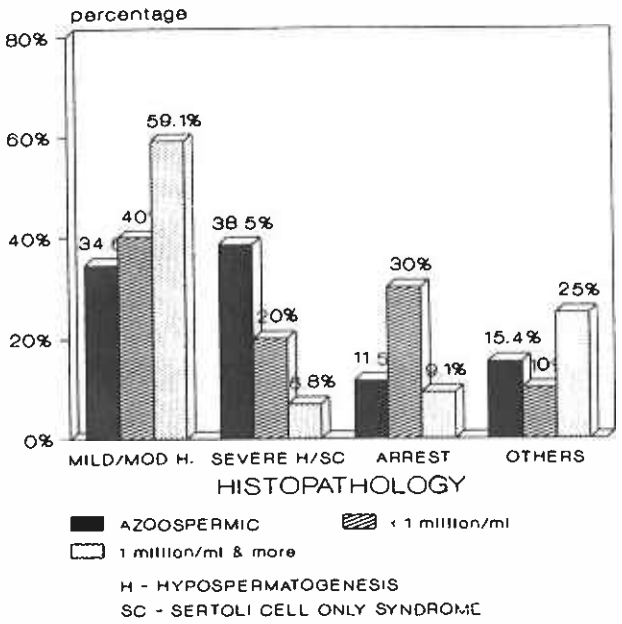


Fig 9. – LH-Histo Correlation (N = 68)

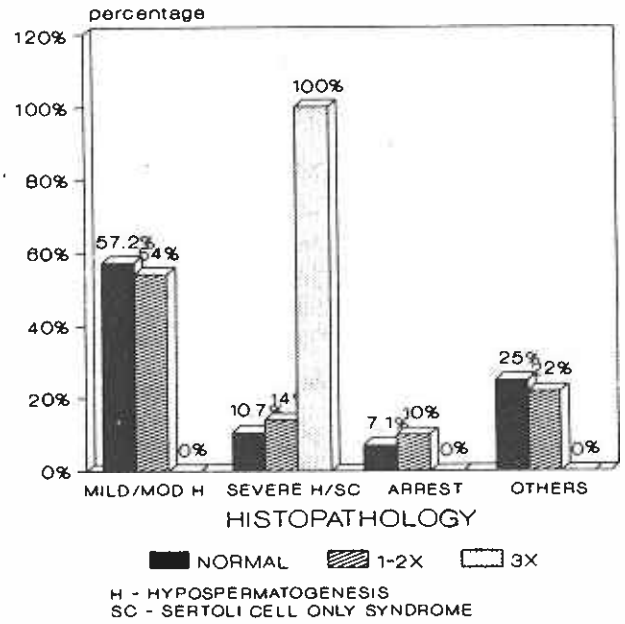


Fig 8. – FSH-Histo Correlation (N = 94)

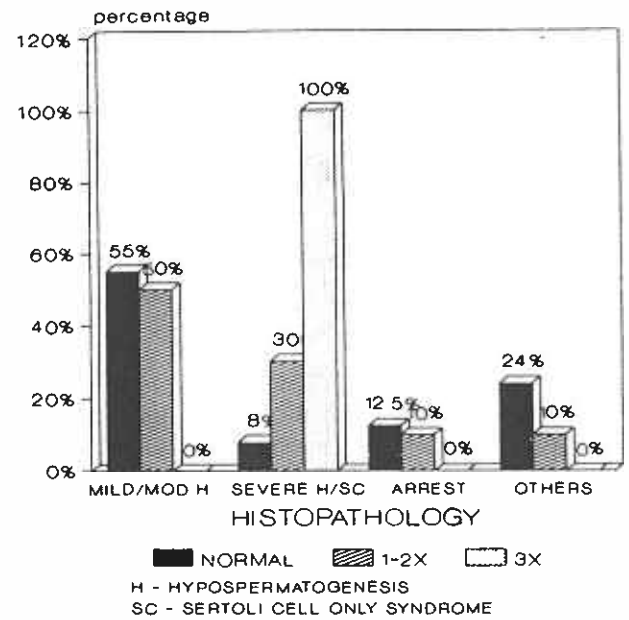
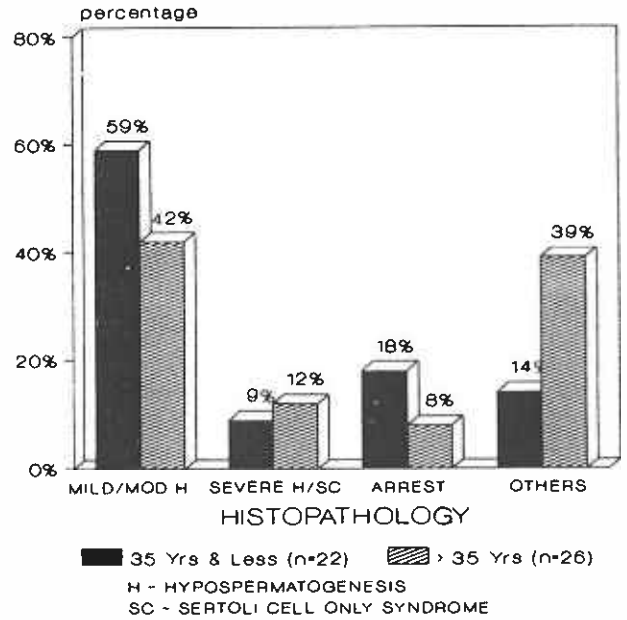


Fig 10. – Age/Varicocele on Histo (N = 48)



suggest that if varicocele was the sole cause, it could affect the contralateral testis as badly as the ipsilateral side.

Grade of Varicocele and Histology: There was little correlation between the grade of varicocele and the severity of the lesion.

Grade of Varicocele and Size of Testis (Fig 11): Smaller testicles were usually found with a higher grade of varicocele. This was true for both the ipsilateral and contralateral sides.

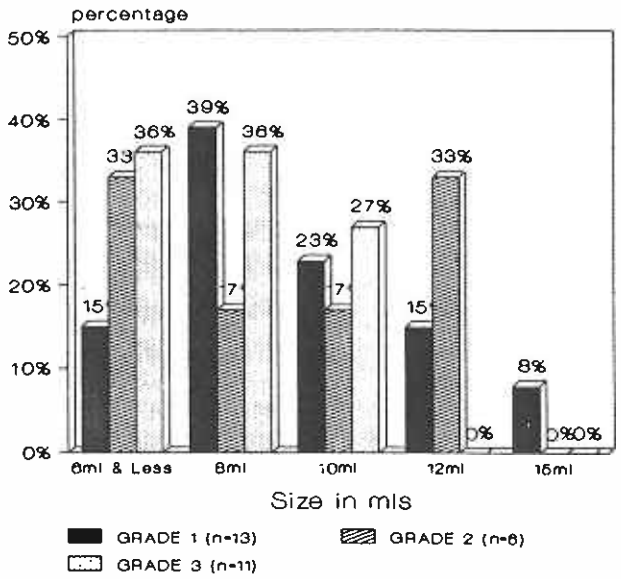
MANAGEMENT

General Advice and Support: The management of patients attending the male infertility clinic included inquiry into habits that might affect spermatogenesis and conception, such as the type of underwear worn, the optimal timing of intercourse and difficulties during intercourse, social habits like drinking and smoking, etc. This led to counselling and advice when appropriate.

Hormonal Treatment: Those with mild or moderate hypospermatogenesis were treated with clomiphene/tamoxifen. Several were referred for assisted conception programmes, eg. sperm separation/concentration techniques followed by AIH, IVF-ET, GIFT, etc.

Surgical Treatment: Patients with varicoceles had their varicoceles ligated at the time of the testicular biopsy procedure. The patient with bilateral congenital absence of the vas who had fairly normal testicular biopsies underwent surgery with the implantation of an artificial sperm reservoir so that sperm could be aspirated for assisted conception programmes. The other patient with a unilateral absence of the right vas, mild hypospermatogenesis and left severe hypospermatogenesis was offered a cross-over vaso-epididymostomy. A bypass right vaso-epididymostomy was done for a patient when vasography revealed a block at the vas distal (ie. prostate end) to the right epididymis.

Fig 11. – Grade Varicocele on Size (Ipsilateral Testis) (N = 30)



AID: Those with severe hypospermatogenesis, germ cell aplasia, extensive sloughing of the tubules and complete spermatogenic arrest were referred for AID.

DISCUSSION

Clinical examination, semen analysis and hormonal studies without testicular biopsy frequently give insufficient information on which to plan rational therapy for male subfertility patients.

Jequier (1986) reported that often in germinal aplasia (Sertoli-cell only syndrome), the testicular size was not markedly reduced[5]. This could lead to diagnostic and prognostic difficulties if size alone was used for evaluation. In our study, the testicular size gave a general indication of the severity of the histopathology. This was not precise (particularly in the intermediate range) and could only serve as a guide towards further evaluation.

Meihard et al (1973) showed that the histology in both azoospermic and oligospermic male infertility patients ranged from normal to a complete loss of germinal tissue[4]. Our study revealed similar results. However, it also showed that patients with a sperm density of 1 million/ml or greater tend to have a better testicular histology. Even if Spark's (1988)[6] classification was utilised and the "Extreme Oligospermia-Azoospermia" category (ie. those with sperm densities at 5 million/ml or less) was being considered, it was those with sperm densities less than 1 million/ml that accounted for most of the severe cases of hypospermatogenesis. With this "EOA category", those with sperm densities of 1 million/ml or greater usually had better biopsy findings, indicating that perhaps the best cut-off point for a working classification should be 1 million/ml.

The majority of infertile patients with testicular pathology had normal or just slightly raised gonadotrophin levels apparently because the extent of testicular damage was not sufficiently great enough to cause an increase in gonadotrophin secretion. Only in those patients with severe hypospermatogenesis, germinal aplasia, extensive sloughing or a type of severe maturation arrest were the FSH levels likely to be elevated. A rise of plasma FSH in patients with idiopathic oligospermia would therefore portend extensive germ cell damage and a guarded prognosis in terms of restoration of fertility[7]. Our study showed that a normal or raised FSH/LH could be associated with all histological types and it becomes only useful when it was raised more than 3 times normal, in which case a testicular biopsy may not then be required.

The use of FSH per se in assessing the severity of the testicular lesion was further complicated by the fact that there are actually two forms of germinal aplasia. The first is where the FSH was grossly elevated and due to decreased or absent inhibin production. The second but less common type of germinal aplasia occurred in the presence of a normal FSH and likely normal inhibin production[8]. In late maturation arrest, testicular size and FSH level might be all within normal limits. This might cause confusion if the evaluation of male infertility patients did not include a testicular biopsy. Our study confirmed this.

Of the many pharmacotherapeutic agents used in patients with oligospermia, the anti-estrogen, clomiphene citrate has gained the most widespread acceptance. Clomiphene citrate has a favourable effect on sperm count in some oligospermic men. Improvement in semen quality in as many as 75% of patients has been reported, as well as pregnancy rates as high at 40%[9]. Clomiphene has been shown to be of no use in patients with high FSH levels. Serum FSH was thus used to screen out potential non-responders. However, with the finding that severely unfavourable testicular histopathology may be associated with normal FSH, the use of testicular biopsy as pre-treatment screening would be more appropriate. The severity of the hypo-spermatogenic state of the gonad is inversely related to the probability of future restoration of fertility. End stage tubular changes, germinal aplasia and marked maturation arrest augurs a poor response to most therapeutic manoeuvres including clomiphene therapy. The use of biopsy to evaluate the cause of treatment failure has an even greater role. Definitely this will assist in the exclusion of patients with unfavourable histology from the inconvenience of further treatment and subjection to therapeutic attempts with higher or prolonged doses of clomiphene or other forms of gonadotrophin therapy.

In certain clinical situations, testicular biopsy could be considered established. First, it can differentiate the azoospermia due to obstruction from that due to primary testicular failure. A normal biopsy in an azoospermic patient with normal FSH would point to a failure of sperm transport and clearly indicates the need for formal testicular exploration, vasography and possible vasovasostomy or vaso-epididymostomy[10]. In this category of patients, percutaneous biopsy could well have its greatest value as it is least invasive prior to the actual scrotal exploration. Secondly, in patients not having had a previous biopsy and scheduled for surgical correction for obstructed vas, a testicular biopsy would be essential for assessing the possibility of success. Also, in cases of post-inflammatory obstruction, there may be unsuspected damage to the germinal epithelium due to orchitis which could substantially reduce the chances for restored fertility. Thus, unnecessary restorative or bypass surgery could be avoided in those with proven obstruction if biopsy showed severe destruction in both testicles[11].

In patients with a varicocele, it could serve as prognostic guide for the restoration of fertility after varicocelectomy. If there was initial severe damage to spermatogenesis due to varicocele, it may be up to two years following surgery before there is any response[12]. This would underscore the need for long term follow-up in these patients. Also, a case could be made for the theoretical value of testicular biopsy in the evaluation of the efficacy of a particular mode of treatment.

Finally, biopsy should serve an important role in those with a hopeless prognosis and would provide the justification for withholding therapy, curtailing therapy already in progress or seeking alternative solutions eg. AID or adoption.

CONCLUSION

Testicular biopsy can be considered as an important tool in the diagnosis and assessment of the majority of male infertility

cases, being a simple procedure that can be done under regional or general anaesthesia. At the same time, a general scrotal exploration, evaluation of vasal patency and surgical treatment of varicocele if present can be instituted. When used judiciously and intelligently, it must necessarily be a more accurate indicator of the state of the germinal epithelium than determination of plasma FSH/LH levels. It would theoretically have even greater value when pathologists couple microscopic study of the biopsy specimen with a quantitative evaluation of germ cells and Leydig cells[7,13,14].

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REFERENCES

1. Charny CW: Testicular Biopsy - Its value in male sterility. JAMA 1940; 115:1429-32.
2. Scott LS: Infertility in males. Br J Hosp Med 1968; 2:644-7.
3. Garduno A, Mehan DJ: Testicular biopsy findings in patients with impaired infertility. J Urol 1970; 104:871-7.
4. Meihard E, McRae CU, Chisholm GD: Testicular biopsy in evaluation of male infertility. Br Med J 1973; 3:577-81.
5. Jequier AM: Primary testicular disease as a cause of male infertility. In: Infertility in the male. Edinburgh: Churchill Livingstone 1986; 6:52-60.
6. Spark RF: Evaluation of the infertile male. In: The infertile male. NY/ London: Plenum Med Book Co, 1988; 13:191-219.
7. Wong TW, Jones TM: Evaluation of testicular biopsy in male infertility studies. In: Infertility in the male. Edinburgh: Churchill Livingstone 1983; 11:217-48.
8. Mecklenburg RS, Sherins RJ: Gonadotrophin response to LH releasing hormone in men with germinal aplasia. J Clin Endocrinol Metab 1974; 38:1005-8.
9. Sorbie PJ, Perez-Marrero R: The use of clomiphene citrate in male infertility. J Urol 1984;131:425-30.
10. Hargreave TB: Laboratory assessment for male infertility. In: Hargreave TB, Teoh ES. eds. The management of male infertility. Singapore: PG Publishing, 1990: 120-1.
11. Hargreave TB: Value of bilateral testicular biopsy prior to corrective surgery for obstruction. Personal Communication. 1987.
12. Foesta, Ruzza G, Rizzotti A, Lembo A, Valente MI, Mastrogincomo: Varicocele and infertility: Preoperative prognostic elements. J Androl 1984; 5:135-7.
13. Agger P, Johnsen SG: Quantitative evaluation of testicular biopsies in varicocele. Fertil Steril 1974; 29:52.
14. Jones TM, Amarose AP, Lebowitz M: Testicular chromosomal mosaicism and infertility. J Clin Endocrinol Metab 1976; 42:888-93.