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ROLE OF TESTICULAR BIOPSY IN THE EVALUATION OF MALE INFERTILITY

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Objective: To evaluate the role of testicular biopsy in the management of male infertility.

Patients and Methods: All male patients who had testicular biopsy as part of management of infertility at our institution between 1991 and 2005 were retrospectively reviewed. Testicular biopsy findings were correlated with clinical findings, semen analysis and hormone levels.

Results: In total, 472 patients with a mean age of 31 years (range 18 – 49 years) were subjected to testicular biopsy. Normal spermatogenesis was found in about 16% of the patients. Germ cell aplasia and peritubular fibrosis were found in 158 (33.5%) patients with atrophic testes (volume <14 mls). Azoospermia was seen in 173 (36.6%) patients with different histological grades of spermatogenesis, while oligospermia was found in 268 (56.8%) patients, most of whom had hypospermatogenesis or maturation arrest. About 6% of our patients had testicular inflammation. The serum follicle stimulating hormone (FSH) in patients with germ cell aplasia was significantly elevated. About one-third of oligospermic men had normal FSH levels.

Conclusion: Testicular biopsy is simple and provides diagnostic and prognostic information for the patient and helps in planning treatment.

Key Words: testis, biopsy, male, infertility, serum FSH and semen analysis.

INTRODUCTION

Worldwide, infertility is a common and distressing problem. It is a cause of emotional and medical problems for the infertile couple[1,2]. Although in many countries, including Nigeria, society often holds the woman responsible for the infertility of a couple, male factors are responsible in about 40% of all couples[3]. Therefore, a complete evaluation of the male partner, especially of the status of spermatogenesis, is important.

Semen analysis is fundamental to the clinical evaluation, but is not a reliable indicator of spermatogenesis, because it is associated with substantial variability in sperm count due to technical errors of collection, method and equipment used for analysis[3]. The measurement of serum follicle stimulating hormone (FSH) is useful in differentiating between obstructive and non-obstructive azoospermia, but does not predict the presence of sperm cells in testicular tissue.

Quantitative testicular biopsy offers an objective assessment of seminiferous epithelium, thus providing significant prognostic information and spermatozoa for assisted reproductive techniques[4,5]. It can predict the sperm output and differentiate between obstructive and non-obstructive azoospermia[4]. In non-obstructive azoospermia, the presence of spermatids on testicular histology is an important indicator of the success of testicular sperm extraction (TESE) and intra cytoplasmic sperm injection (ICSI)[6]. Abnormal testicular histology is also an adverse pre-operative factor for the outcome of epididymo-vasostomy[7].

Percutaneous testicular biopsy may be used for isolation, purification and assessment of viability of spermatogenic cells in azoospermic men[8]. However, studies have demonstrated that open biopsies are required to achieve an optimal chance of finding the rare foci of testicular spermatozoa within the poorly functioning gonads of men with non-obstructive azoospermia[6,9]. In recent years, the diagnostic role of testicular fine needle aspiration cytology in male infertility has been popularized, because it is simple, reliable and relatively non-invasive[10].

Infertility is a common problem in our daily clinical practice. Many of these patients achieve pregnancy before elaborate investigations are performed. However, in a few the cause of infertility could not be established at the end of these investigations. We retrospectively reviewed 472 patients who had testicular biopsy to reappraise the value of testicular biopsy in the management of male infertility.

PATIENTS AND METHODS

In this study we retrospectively reviewed the case notes of all patients who were subjected to testicular biopsies as part of management of male infertility at the Urology Division, Department of Surgery, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria, between 1991 and 2005. The patients presented with a history of infertility for a variable period of time. The indications for biopsy were azoospermia or subnormal semen variables when history, physical examination and other investigations failed to explain the infertility. Testicular biopsy was also performed on patients undergoing varicocelectomy. Bilateral open testicular biopsy was done in all cases. The tissue was fixed in Bouin's solution and examined in the histopathology laboratory. The histological findings were analysed and correlated with clinical findings, semen analysis and hormonal levels.

RESULTS

During the study period, 472 patients with a mean age of 31 years (range 18 – 49 years) were subjected to testicular biopsies and the results were similar in both testes. Normal spermatogenesis was found in 75 (15.9%) patients (Table 1). Peritubular fibrosis was found in 29 (6.2%) patients including 4 with tuberculous orchitis.

Germ cell aplasia and peritubular fibrosis were found in 158 (33.5%) patients with a testis volume less than 14 mls. 168 (35.6%) patients with varicocele had maturation arrest and hypospermatogenesis. Normal spermatogenesis was found in about 60% of patients with azoospermia and a previous history of urethritis or epididymal indurations. Overall, azoospermia was seen in 173 (36.6%) patients with a histological pattern ranging from normal spermatogenesis to germ cell aplasia. Oligospermia was found in 268 (56.8%) patients, most of whom had hypospermatogenesis or maturation arrest on histology.

The serum FSH in patients with azoospermia and normal spermatogenesis was normal and ranged between 2.1 and 4.8 IU/L, while in patients with germ cell aplasia it was 8.6 to 19.2 IU/L. About one-third of oligospermic men had normal FSH. None of the patients had intratubular neoplasia.

DISCUSSION

As in other studies reported in the literature, the indications for testicular biopsy in this study were mainly azoospermia and oligospermia[11,12]. Some patients had testicular biopsy at the time of varicocele surgery in order to assess the state of seminiferous epithelium and provide prognostic information to the patient. The most prevalent histologic pattern was hypospermatogenesis, which together with maturation arrest constituted the main histologic pattern seen in patients with oligospermia. Increased apoptosis was observed in these patients compared to those with obstructive azoospermia, indicating a prominent role of this form of programmed cell death in male infertility[13]. In 133 patients (28.2%) in our study the seminiferous tubules contained only Sertoli cells. This histological

Table 1: Correlation of Testicular Histology and Semen Analysis

Testicular Histology	Azoospermia	Oligospermia	Normal sperm count	Total (%)
Normal spermatogenesis	32	37	6	75 (15.9)
Hypospermatogenesis	12	136	18	166 (35.2)
Maturation arrest	6	60	3	69 (14.6)
Germ cell aplasia	119	14	0	133 (28.2)
Peritubular fibrosis	4	21	4	29 (6.1)
Total	173	268	31	472 (100)

appearance was associated with marked elevation of serum FSH and was often found in patients with a history of torsion, orchitis or testicular maldescent[14,15].

The prevalence of peritubular fibrosis in our study (6.2%), more commonly due to inflammation, was lower than that reported from Ibadan (22.4%)[16] but higher than in developed countries[17,18]. This suggests that inflammatory conditions may contribute more to infertility in developing countries. In this study, the commonest histologic pattern seen was hypospermatogenesis. However, a more severe reduction in spermatogenic capacity was found in azoospermic men.

In some patients clinical examination, semen analysis and hormone studies may not provide a guide to the severity of the lesion, thus making testicular biopsy necessary, while in others it complements other predictors. Testicular size was the most important predictor of testicular pathology, with the worst changes in smaller testes[12,18]. However, in our study as in other reports, the correlation between testicular size and testicular pathology was imperfect[15,19]. Patients with large testes may be azoospermic, while a few with small testes may have normal spermatogenesis[15,19]. The pattern with varicocele is characterized by maturation arrest and hypospermatogenesis, and biopsy helps to predict the outcome of treatment[20,21].

Serum FSH helps to differentiate between obstructive and spermatogenic dysfunction as the possible cause of azoospermia[22]. As reported by others, an elevation of serum FSH correlates with the appearance of Sertoli cell only tubules[11,15,23]. However, normal FSH can be found in germinal aplasia or maturation arrest[6]. In maturation arrest, the testes are often of normal size, thus the diagnosis cannot be made without biopsy. In azoospermic men, an obstruction cannot be excluded, even if FSH is substantially elevated, provided that at least one of the testes is of normal size[23]. Similarly, normal FSH even in azoospermic men does not exclude primary testicular disease[22]. Recently it has been suggested that serum levels of inhibin-B in combination with serum FSH is a more sensitive marker than serum FSH alone for impaired spermatogenesis in men[24,25]. However, the prediction of the quantity of spermatogenesis is not superior to that of FSH alone[25].

In our patients, azoospermia was represented by all histological patterns, while oligospermia was represented mainly by hypospermatogenesis and maturation arrest. In some patients, the testicular disorder was not widespread in the testes and thus not severe enough to result in azoospermia or oligospermia. In this study, normal spermatogenesis in azoospermic men indicated bilateral ductal obstruction. The majority of these patients were treated by epididymo-vasostomy. However, a few were referred for assisted reproductive techniques when the chance for success of sperm retrieval with in-vitro fertilization exceeded that for surgical treatment, as we do not have

facilities for cryopreservation and assisted reproductive techniques in our center[6,22].

Testicular causes of azoospermia are generally irreversible, with the exception of impaired spermatogenesis associated with varicocele. Testicular biopsy in these patients provides prognostic information, because sperm retrieval is proportional to spermatogenic activity in the examined histological samples[6]. Some studies indicate a strong association between subfertility and subsequent development of carcinoma-in-situ of the testes[26]. There was no record of intra-tubular neoplasia in our study.

In this study, patients with germ cell aplasia had azoospermia or severe oligospermia but sperm count alone was not a reliable indicator of spermatogenesis. To distinguish between obstructive and non-obstructive azoospermia in patients with normal testicular size and normal serum FSH levels, diagnostic testicular biopsy is indicated. Primary testicular disease is always associated with a marked elevation of serum FSH level, which is an indicator of abnormal spermatogenesis. Testicular biopsy is not necessary in these patients. However, if testicular sperm extraction (TESE) is taken into consideration, testicular biopsy can be performed to determine whether spermatozoa are likely to be retrievable in the future by needle aspiration or open biopsy. The detection of untreatable conditions on histological examination of the testes should spare the couple the distress of attempting ineffective therapies.

In conclusion, testicular biopsy is a simple method which provides diagnostic and prognostic information for the patient and may help in planning treatment.

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RESUME

ROLE DES BIOPSIES TESTICULAIRES DANS L'EVALUATION DE L'INFERTILITE MASCULINE

Objectif : L'évaluation du rôle de la biopsie testiculaire dans la prise en charge de l'infertilité masculine.
Patients et méthodes : Tous les patients masculins qui ont eu une biopsie testiculaire en tant qu'élément de la prise en charge de l'infertilité à notre établissement entre 1991 et 2005 ont été rétrospectivement passés en revue. Les résultats de biopsie testiculaires ont été corrélés avec les résultats cliniques, l'analyse de sperme et les niveaux d'hormones.
Résultats : Au total, 472 patients présentant un âge moyen de 31 ans (extrêmes de 18 à 49 ans) ont été soumis à la biopsie testiculaire. Une spermatogénèse normale a été trouvée chez environ 16% des patients. L'aplasie des cellules germinales et la fibrose peritubulaire ont été trouvés chez 158 (33.5%) patients avec des testicules atrophiques (de volume <14 ml). L'azoospermie a été vue chez 173 (36.6%) des patients présentant différentes catégories histologiques de la spermatogénèse, alors que l'oligospermie a été trouvée chez 268 (56.8%) patients; la plupart de ces patients ont une hypo spermatogénèse ou un arrêt de maturation. Environ 6% de nos patients ont une l'inflammation testiculaire. L'hormone follico-stimulante (FSH) sérique chez les patients avec aplasie des cellules germinales a été sensiblement élevée. Environ un tiers d'hommes oligospermiques ont des niveaux normaux de FSH.
Conclusion : La biopsie testiculaire est simple et fournit des informations diagnostiques et pronostiques pour le patient et aide dans la planification du traitement.
Mots Clés : testicule, biopsie, mâle, infertilité, sérum FSH et analyse de sperme.

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