



## RESEARCH PAPER

## OPEN ACCESS

## Testis histopathological changes in fertility disorders

Mohammad Taghizadieh<sup>1</sup>, Fatemeh Afshari<sup>1</sup>, Omid Karami-Khaman<sup>2\*</sup>

<sup>1</sup>Department of Histopathology, Tabriz Branch, Islamic Azad University, Tabriz, Iran

<sup>2</sup>Tabriz Branch, Islamic Azad University, Tabriz, Iran

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### Abstract

Three hundred and twelve male patients undergoing testicular biopsy. Following biopsy the samples was sent to the Qaem pathology laboratory, then the samples was fixing in formalin and dehydrated by alcohol and clearing with xylol and paraffin blocks then prepared. After preparing the sections with microtome, samples were stained by hematoxylin and eosin (H&E) and studied by light microscopy. Histopathological results indicated that the most frequent histopathologic patterns of samples were Germ Cell Aplasia or Sertoli Cell Only Syndrome. Histopathological patterns of testicular biopsy are different from one part of the world to another, and related to many factors.

\* **Corresponding Author:** Omid Karami-Khaman ✉ [karamiomid2013@gmail.com](mailto:karamiomid2013@gmail.com)

## Introduction

Infertility in men means inability to fertilization after one year unprotected sexual relationship. Approximately, 15% of the couples suffer from infertility. It is estimated that 40% of men and women disorders cause to infertility and in the remainder, both gender have disorder (Tanagho and Mcaninch, 2008).

Although male infertility is a major cause of infertility, and it is liable to half of all cases of infertility (Irvine, 1998), But investigations on infertility have always concern female pathological causes while male pathological causes that were leading to infertility, still generally unknown. The evaluation of the infertile male includes a thorough clinical history taking and physical examination, semen analysis, hormonal assay, and search for antisperm antibody. Additional tests include transrectal ultrasonography, vasography and testicular biopsy.

Also men infertility and histopathologic findings resulted from biopsy is different from one part to another in the world due to social habits, genetics and environmental factors like infections, chemical substances and radiation and heat (Saradha and Mathur, 2006).

Men infertility is a personal and social problem. Assisted reproductive technology (ART) has offered treatment methods for elimination and reduction of infertility in the men. However, yet in most of the authentic ART centers, the birth-life index is less than 45 percent. In the other hand, curative treatment in the infertile men (pharmacologic or surgery) could have used in a few men suffering from disorder in semen that it mostly unknown (Dimitriadis *et al.*, 2010).

Different factors cause to infertility in men. These factors can be diagnosed by description, physical examination, and semen analysis and hormone test in addition to auxiliary tests (Sigman *et al.*, 1997). Increase of age influences infertility. The modern

societies tend to delay in child birth and fertility and reproduction is decreased in middle of thirtieth and consequently in late fortieth and fiftieth. So, it has led to increase of infertility in developing countries (Sharov *et al.*, 2008).

It was reported that up to 7 and 15% of men suffering from oligospermia and azoospermia with testis failure, possess minor deletion in one or several genes on the long part of Y chromosome. Several regions of this chromosomes involved in the failure of spermatogenesis have been identified that are known as AZFc. DAZ gene deletion in the AZFc is the most common deletion in infertile men (Gatta *et al.*, 2010). Function of leydig cells intracellular organelles causes to disorder in various stages of spermatogenesis that it can also cause a significant decrease in leydig cells and hypospermatogenesis and male infertility (Fan *et al.*, 1996- Kaczmarek *et al.*, 2011).

It was reported that the histopathological patterns following testis biopsy was as: 14% of cases was reported as normal spermatogenesis; 29% as hypospermatogenesis; and 12% was as GCMA, mostly at the level of primary spermatocytes. The Sertoli cell only syndrome and the seminiferous tubule hyalinization categories were each reported in 16 percent. Nine percent of them showed a mixed pattern, and discordant pattern was seen in 5% of cases (Abdullah and Bondagji, 2011).

Testis biopsy could offer exact clinical diagnosis in infertile men investigation, and aids to treatment method selection in most of the infertility disorders. By special technical methods, small part of testis is removed and examined histopathologically and the seminiferous tubules and cellular composition can be determined. Testis biopsy is most helpful in patients suffering azoospermia. Since, in these individuals differentiation between lack of sperm production and reproductive tract blockage problem is difficult. Testis biopsy gives us important information in this regard (Ahamad *et al.*, 2010). Therefore, it seems important to find and use drugs for treatment of fertility with unknown causes.

### Material and Methods

In this research we used pathological and statistical methods. This study was a retrospective cross-sectional research.

#### Pathological method

All samples obtained from 312 patient's biopsy, during 2009.4.5 to 2013.5.21 in the Gaem Pathology laboratory were studied. Unilateral or bilateral testis biopsy was taken by local anesthesia in all patients participated in this study. The samples were transferred to the pathologic laboratory in bouin's fixation solution. All biopsy specimens were stained after initial processing with Hematoxylin & Eosin (H&E) and examined under a light microscope.

### Results

Unilateral or bilateral testis biopsy were performed in 312 patients from 2009.4.5 to 2013.5.21. Most of those patients suffering from primary infertility or secondary infertility referred to the clinic because of oligospermia and azoospermia.

Their ages ranged from 19 to 47 years with a mean age of  $35 \pm 0.47$  (Table 1) (Fig. 1).

Of the 312 patients, 292 patients (93.6%) complained to their original non-primary infertility, 8 patients (2.6%) suffered from unknown secondary fertility, 3 patients (1.0%) complained about feeling a mass in the testis and 9 cases (2.9%) had no particular complain (Table 2, Fig. 2).

**Table 1.** Frequency distribution of patients that were undergoes testis biopsy.

Age	Numbers	Percent
19	11	3.5
21	11	3.5
22	11	3.5
24	22	7.1
27	11	3.5
28	11	3.5
29	11	3.5
30	11	3.5
31	11	3.5
33	22	7.1
35	22	7.1
36	21	6.7
37	11	3.5
39	11	3.5
40	22	7.1
41	11	3.5
42	11	3.5
45	20	6.4
46	20	6.4
47	31	9.9
Total	312	100

**Table 2.** Primary complaint frequency.

Primary complaint	Numbers	Percent
Primary infertility	292	93.6
Mass feeling	3	1
Secondary infertility	8	2.6
Without complaint	9	2.9
Total	312	100

**Table 3.** Biopsy site.

Biopsy site	Numbers	Percent
Right testicle	133	42.6
Left testicle	155	49.7
Both testicles	11	3.5
unknown	13	4.2
Total	312	100

**Table 4.** Frequency of histopathologic patterns of biopsies.

Histopathologic pattern	frequency	percent
Germ cell aplasia (sertoli cell only syndrome)	82	26.3%
Spermatocytic arrest complete	28	9%
Spermatocytic arrest incompele	37	11.9%
General fibrosis	17	5.4%
Mixed atrophy	68	21.8%
orchitis	8	2.6%
Inappropriate sample	10	3.2%
Lydig cell tumor	1	0.3%
Normal	61	19.6%
Total	312	100%

Biopsy specimens were obtained from the right testis in 133 patients (42.6%), and in 155 patients (49.7%) from the left testis, and in 11 patients (3.5%) bilateral biopsy was done and in 13 cases (4.2%) it was unknown (Table 3, Fig. 3).

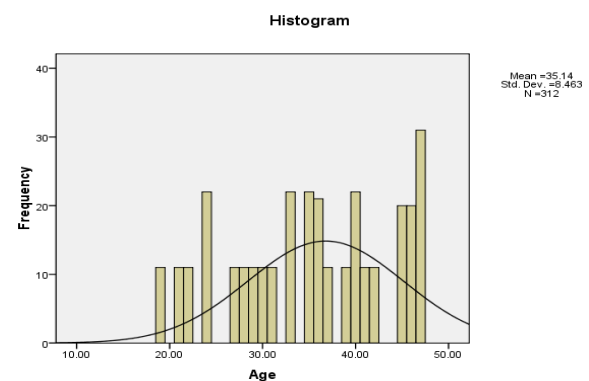
*Histopathologic study of the cases in this study show the following results*

82 cases (26.3%) sertoli cell only syndrome (SCO) = Germ cell aplasia (Fig. 5), 68 cases (21.8%) mixed atrophy, 37 cases (11.9%) incomplete spermatocytic arrest, 28 cases (9%) complete spermatocytic arrest (Fig. 6), 17 cases (5.4%) general fibrosis, 8 cases (2.6%) orchitis, 10 cases (3.2%) were unfit, 61 cases (19.6%) subjects were normal (Figure7), 1 case (0.3%) showed leydig tumor cells ( Table 4).

### Discussion

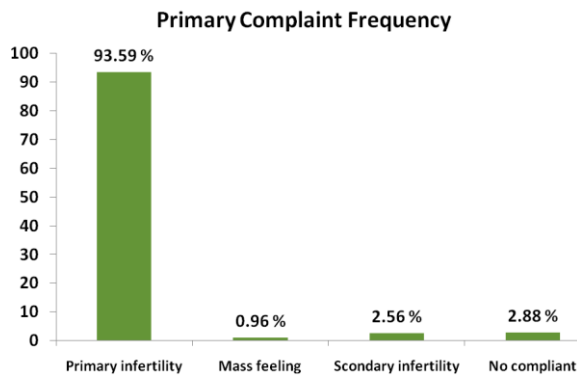
Infertility is a serious social problem in developed and developing countries. In general, almost half of the non-reproductive cases are associated with male factors (Parikh *et al.*, 2012). Men infertility and histopathologic findings resulted from biopsy is different from one part to other in the world due to social habits, genetics and environmental factors like

infections, chemical substances and radiation and heat (Saradha and Mathur, 2006).



**Fig. 1.** Histogram of age frequency in understudy patients.

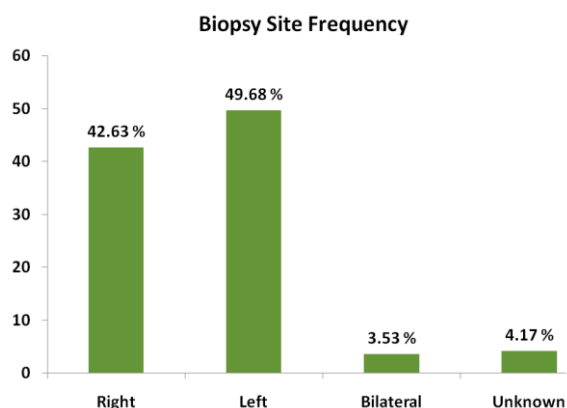
Testis biopsy is a diagnostic key for testis causes of infertility. Though, it is not only parameter for assessment of testis histopathologic model but it is a powerful method for prediction of finding sperm in testis for uses of the sperm in fertilization of the ovule (Mclachlan *et al.*, 2007).



**Fig. 2.** Histogram of primary complaint frequency.

Testis biopsy is important evaluation method in men at risk of testis cancer or carcinoma in situ (Abdullah and Bondagji, 2011). Testis biopsy can be done under local anesthesia or general anesthesia as transcutaneous needle or open biopsy from one point or more points (Nistal *et al.*, 1999). The results of this study are different with some national and international studies and similar some of them.

Our results indicated that the most frequent testis biopsies microscopic view was Germ cell aplasia or Sertoli cell only syndrome (SCO) that was observed in 82 patients (26.3%) of the total subjects. These results are consistent with some previous studies (Al-Rayess and Al-Rikabi, 2000- Jamal and Mansoor, 2001- Kim *et al.*, 1997- Nistal *et al.*, 1999- Thomas and Jamal, 1995). On the other hand, these results are inconsistent with some other studies (Abdullah and Bondagji, 2011- Alaa, 2012).



**Fig. 3.** Histogram of biopsy site frequency.

SCO is an irreversible change that it could be due to several underlying causes, including testis cryptorchidism, orchitis, after radiation or

chemotherapy, and androgen and estrogen therapy and can also be a result of chronic liver pathology (Nistal *et al.*, 1999).

This study indicated that in 65 cases (19.0%) spermatocytic arrest histopathologic changes that it was the third histopathologic change in this study in contrary to a foreign research that this view was most frequent (Alaa, 2012).

The second view was commonly mixed atrophy patterns in our histopathological study (68 cases) and 21.8 % which is consistent with a study done by foreigners (McLachlan *et al.*, 2007). In this research, General fibrosis view was observed in 17 cases (5.4%) of the subjects that was inconsistent with the results of foreign studies (Al-Samawi *et al.*, 2009- Nagpal *et al.*, 1993), where a high percentage of 22.4 % has been reported. In the studies it was cited that in the previous inflammatory process as the previous orchitis, the main role is creating this pattern.

In our study, 61 cases (19.6 %) showed a normal pattern as the second common pattern. Generally, the results of national and international research show that men infertility and histopathologic findings on testis biopsies are different significantly from one part to other parts of the world. The difference between this study and other studies is not well understood. Although, these studies refer to different factors such as social habits, environmental and genetic factors that they need to expanded research.

### Conclusion

In general, our study showed that the most common histopathologic view of testis biopsies was view of Germ cell Aplasia and sertoli cell only syndrome which in this case could be due to cryptorchidism, orchitis, exposure to radiation and chemotherapy, as well as the internal problems that necessitate more comprehensive study in the near future.

**References**

- Abdullah L, Bondagji N.** 2011. Histopathological Patterns of Testicular Biopsy in Male Infertility: A Retrospective Study from a Tertiary Care Center in the Western Part of Saudi Arabia. *Urology annals* **3**, 19-23.  
<http://dx.doi.org/10.4103/0974-7796.75867>
- Ahamad MSU, Chowdhury BO, Zobair M.** 2010. Testicular Fine Needle Aspiration in Male Infertility: A Review. *Journal of Chittagong Medical College Teachers' Association* **21**, 62-65.  
<http://dx.doi.org/10.3329/jcmcta.v21i1.7681>
- Al-Rayess MM, Al-Rikabi AC.** 2000. Morphologic Patterns of Male Infertility in Saudi Patients. *Saudi Medical Journal* **21**, 625-628.
- Al-Samawi AS, Al-Malas NA, Jibrel SO.** 2009. Histologic Pictures of Male Infertility in Yemeni Patients. *Saudi Medical Journal* **30**, 652-655.
- Alaa HR.** 2012. Testicular Biopsy in Azoospermic Men: A Study of the Morphological Patterns in Duhok City and an Attempt toward the Development of a New Evaluation System. *Duhok Medical Journal* **6**, 253-258.
- Dimitriadis F, Tsambalas S, Tsounapi P, Kawamura H, Vlachopoulou E, Haliasos N, Gratsias S, Watanabe T, Saito M, Miyagawa I.** 2010. Effects of Phosphodiesterase-5 Inhibitors on Leydig Cell Secretory Function in Oligoasthenospermic Infertile Men: A Randomized Trial. *BJU international* **106**, 1181-1185.  
<http://dx.doi.org/10.1111/j.1464-410X.2010.09243.x>
- Fan CY, Pan J, Chu R, Lee D, Kluckman KD, Usuda N, Singh I, Yeldandi AV, Rao MS, Maeda N, Reddy JK.** 1996. Hepatocellular and Hepatic Peroxisomal Alterations in Mice with a Disrupted Peroxisomal Fatty Acyl-Coenzyme a Oxidase Gene. *J Biol Chem* **271**, 24698-24710.
- Gatta V, Raicu F, Ferlin A, Antonucci I, Scioletti AP, Garolla A, Palka G, Foresta C, Stuppia L.** 2010. Testis Transcriptome Analysis in Male Infertility: New Insight on the Pathogenesis of Oligo-Azoospermia in Cases with and without Azfc Microdeletion. *BMC genomics* **11**, 401.  
<http://dx.doi.org/10.1186/1471-2164-11-401>
- Irvine DS.** 1998. Epidemiology and Aetiology of Male Infertility. *Human Reproduction* **13 Suppl 1**, 33-44.  
[http://dx.doi.org/10.1093/humrep/13.suppl\\_1.33](http://dx.doi.org/10.1093/humrep/13.suppl_1.33)
- Jamal AA, Mansoor I.** 2001. Morphological Profile of Testicular Biopsies Associated with Infertility. *Saudi Medical Journal* **22**, 992-994.
- Kaczmarek K, Studencka M, Meinhardt A, Wiczerzak K, Thoms S, Engel W, Grzmil P.** 2011. Overexpression of Peroxisomal Testis-Specific 1 Protein Induces Germ Cell Apoptosis and Leads to Infertility in Male Mice. *Molecular biology of the cell* **22**, 1766-1779.  
<http://dx.doi.org/10.1091/mbc.E09-12-0993>
- Kim ED, Gilbaugh JH, Patel VR, Turek PJ, Lipshultz LI.** 1997. Testis Biopsies Frequently Demonstrate Sperm in Men with Azoospermia and Significantly Elevated Follicle-Stimulating Hormone Levels. *The Journal of urology* **157**, 144-146.  
[http://dx.doi.org/10.1016/S0022-5347\(01\)65308-4](http://dx.doi.org/10.1016/S0022-5347(01)65308-4)
- Mclachlan R, Rajpert-De Meyts E, Hoesli-Hansen C, De Kretser D, Skakkebaek N.** 2007. Histological Evaluation of the Human Testis—Approaches to Optimizing the Clinical Value of the Assessment: Mini Review. *Human Reproduction* **22**, 2-16.  
<http://dx.doi.org/10.1093/humrep/del279>
- Nagpal BL, Manjari M, Kapoor K, Dhaliwal US.** 1993. Testicular Biopsy in Cases of Male Infertility: A Retrospective Study. *J Indian Med Assoc* **91**, 171-174.

**Nistal M, Riestra ML, Galmés-Belmonte I and Paniagua R.** 1999. Testicular Biopsy in Patients with Obstructive Azoospermia. *The American journal of surgical pathology* **23**, 1546-1554.

<http://dx.doi.org/10.1097/00000478-199912000-00013>

**Parikh U, Goswami H, Deliwala K, Shah A, Barot H.** 2012. Testicular Biopsy in Male Infertility: Study of 80 Cases. *Journal International Medical Sciences Academy* **25**, 75-77.

**Saradha B, Mathur P.** 2006. Effect of Environmental Contaminants on Male Reproduction. *Environmental Toxicology and Pharmacology* **21**, 34-41.

<http://dx.doi.org/10.1016/j.etap.2005.06.004>

**Sharov AA, Falco G, Piao Y, Poosala S, Becker KG, Zonderman AB, Longo DL, Schlessinger D, Ko MS.** 2008. Effects of Aging and Calorie Restriction on the Global Gene Expression Profiles of Mouse Testis and Ovary. *BMC biology* **6**, 24.

<http://dx.doi.org/10.1186/1741-7007-6-24>

**Sigman M, Lipshultz LI, Howards SS.** 1997. Evaluation of the Subfertile Male. In: Lipshultz LI and Howards SS, ed. *Male Infertility, Diagnosis and Treatment*. UK, Mosby, 117-140 p.

**Tanagho EA, Mcaninch JW.** 2008. *Smith's General Urology*, McGraw-Hill Medical.

**Thomas J, Jamal A.** 1995. Primary Testicular Causes of Infertility: Do Environmental and Socio-Cultural Factors Have a Role? *Tropical and geographical medicine* **47**, 203-205.