

The evaluation of gonadotropins (FSH, LH) and testicular pathology in infertile men

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Abstract

Background: Azoospermia is the most challenging issue associated with infertility treatment. The aim of this study was to re-examine the relationship between plasma levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) with testicular pathology in azoospermic infertile men visiting the infertility clinic in north of Iran.

Methods: Fifty eligible azoospermic infertile men who had the medical indication of testicular biopsy for sperm retrieval in infertility clinic were included in the study. Plasma FSH and LH were measured by immunoassay. Then a bilateral testicular biopsy using Bouin's solution as a fixative was performed under local anesthesia. The One-way analysis of variance was used to assess the differences between the groups.

Results: The plasma levels of FSH ($p=0.0001$) and LH ($p=0.044$) among infertile men with Sertoli-cell-only syndrome was significantly higher than those with hypospermatogenesis. Also, the plasma levels of FSH among infertile men with maturation arrest was significantly higher than those with hypospermatogenesis ($p=0.003$). There were no statistically significant differences in plasma LH levels between hypospermatogenesis and maturation arrest.

Conclusions: The findings of the present study indicated that the plasma levels of FSH and LH among infertile men with azoospermia testis correlated with the histopathological features. Therefore, it is necessary to emphasize the fact that azoospermic cases with highly-elevated plasma FSH and LH levels could be excluded from separate testicular biopsy as they are not suitable cases for conventional treatments.

Keywords: Azoospermia, FSH, LH, Testicular biopsies

Introduction

Infertility is a significant public health problem, affecting approximately 15.5 per cent of the couples in Babol, Iran (1). It is worth noting that about 50 per cent of the couples experiencing infertility are males (2, 3). It should also be noted that around 15–20% of male infertility is due to azoospermia, which is described as

a sperm concentration with complete absence of sperm from the ejaculate (4, 5). There are many causes leading to azoospermia such as the failure of spermatogenesis and the obstruction of the vas deferens (6-8). The infection of the genital tract is known to damage the spermatogenesis (9, 10). The spermatogenic damage may lead to an increase in the level of plasma follicle-stimulating hormone (FSH) (11). Nevertheless, many infertile men have normal

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level of plasma FSH (12). The measurement of FSH is the most important hormonal evaluation in the management of azoospermic men (13). Similarly, spermatogenic damage is sometimes associated with increased luteinizing hormone (LH) (12). The testicular biopsy is considered as a key tool for the diagnosis and treatment of male infertility (14). Therefore, in order to characterize the hormonal testicular function as well as the testicular pathology in male infertility, we re-examined the relationship between the plasma levels of FSH and LH with testicular pathology in infertile men visiting the infertility clinic in Babol, city in north of Iran.

Materials and Methods

The ethical committee at Babol University of Medical Sciences approved the study protocol (No: MUBABOL.REC.1392.6) and written informed consents were also obtained from all participants.

The inclusion criteria for the study were: no history of diabetes, hypertension, and surgical history. The information regarding the past medical history, social history, physical examination, the results of semen analysis, and the histological evaluation of testicular biopsy were extracted from the medical records of individual patients. The subjects were requested for a complete medical history, physical examinations, at least two semen analyses with more than two weeks interval, which were conducted according to the 2010 World Health Organization guidelines, and gonadotropins (FSH and LH).

Blood samples were obtained for the estimation of the plasma level of FSH and LH in the morning (8-10 a.m.). They were measured by immunoassay, and the results were expressed in ng/mL.

Semen samples were taken through masturbation after a 3-day period of sexual abstinence, and collected in a sterile recipient. Sperm analysis was carried out according to the standards of World Health Organization (15). The ordinary extract bilateral testicular biopsy had to be performed if there was no sperm found by both the wet prep analysis of testis tissue and the microscopic testicular sperm.

Finally, 50 eligible azoospermic infertile men who had the medical indication of testicular biopsy for sperm retrieval were included in this study. It should be noted that all cases were selected from among the patients referring to Fatemehzahra infertility clinic in Babol, The bilateral testicular biopsy, using Bouin's solution as a fixative, was performed under local anesthesia to understand the histopathological condition of the

subjects. The histological findings were divided into three categories: the hypoermatogenic (mild, moderate, and severe), the maturation arrests, and the sertoli-cell-only.

All the results of FSH and LH were expressed as mean $\pm$ standard deviation (S.D.). The One-way analysis of variance was used to assess the differences between the plasma FSH and LH between the groups. P-values less than 0.05 were considered significant.

Results

The mean age of the subjects was 34.8 ± 6.0 , ranging from 25 to 58. The mean duration of infertility was 4.5 ± 2.3 , ranging from 1.5 to 9. Table 1 illustrates that out of 50 azoospermic infertile men, 29 (58.0%) were hypospermatogenesis, 11 (22.0%) were maturation arrest, and only 10 (20.0%) had Sertoli-cell only syndrome, which is according to the results of testicular histology. Also, in azoospermic infertile men with abnormal testicular histology, the mean FSH values were 6.1 ± 5.1 , 15.8 ± 11.8 , and 19.1 ± 8.8 mIU/ml for the hypospermatogenesis, the maturation arrest, and the Sertoli-cell only syndrome, respectively. The plasma FSH levels among azoospermic infertile men with Sertoli-cell-only syndrome was significantly higher than that of hypospermatogenesis ($p=0.0001$). Also, the plasma levels of FSH among infertile men with maturation arrest was significantly higher than that of those with hypospermatogenesis ($p=0.003$). Furthermore, in azoospermic infertile men with abnormal testicular histology, the mean LH values were 5.3 ± 2.4 , 8.2 ± 5.1 , and 8.5 ± 3.8 mIU/ml for the hypospermatogenesis, the maturation arrest, and the Sertoli-cell only syndrome, respectively. The plasma LH levels among azoospermic infertile men with Sertoli - cell only syndrome was significantly higher than that of hypospermatogenesis ($p=0.044$).

Table 1. Plasma FSH and LH levels in azoospermic infertile males with abnormal testicular histology

	Number of Subjects	FSH (miu/ml) Mean $\pm$ SD	LH (miu/ml) Mean $\pm$ SD
Hypospermatogenesis	29	6.1 ± 5.1 *¥	5.3 ± 2.4 £
Maturation arrest	11	15.8 ± 11.8 ¥	8.2 ± 5.1
Sertoli - cell only syndrome	10	19.1 ± 8.8 *	8.5 ± 3.8 £

* $P < 0.0001$; ¥ $p < 0.01$; £ $P < 0.05$

Discussion

Testicular biopsy is performed to differentiate the testicular failure from the obstruction. It is also done for sperm retrieval to be used in assisted reproductive techniques in the case of azoospermic men (16, 17). In addition, in infertile men, the higher plasma FSH is a reliable indicator of damage for the seminiferous epithelial destruction, and is also associated with azoospermia and severe oligozoospermia (18). Therefore, for the initiation of spermatogenesis and the maturation arrest of spermatozoa, the elevation of plasma FSH is necessary. However, the correlation between the disturbances of spermatogenesis and the plasma FSH levels has been unestablished (19). It is suggested that the elevated plasma FSH levels result from the impaired stratum corneum function (20). In our study, in the case of infertile males with Sertoli - cell only syndrome and the maturation arrest, the mean FSH levels were significantly elevated when compared with hypo spermatogenesis cases. In addition, the highest plasma FSH level was observed in infertile males with Sertoli - cell only syndrome. A similar observation was made by De Krester et al. (21) Babu et al. (22), Nistal et al. (23), and Turek et al. (24), demonstrating elevated levels of FSH and Micic (25), and the elevated levels of LH in infertile males with Sertoli-cell only syndrome. However, Weiss et al. (26) found no significantly elevated plasma FSH level and LH in infertile men with Sertoli-cell only syndrome.

One of the limitations of this study was the limited size of the sample. Therefore, it seems vital to conduct further histological and hormonal findings in a large cohort of azoospermic men through precise histological features

Conclusion

The present study demonstrated that azoospermic infertile men with elevated FSH and LH had a Sertoli - cell only feature on histology. Therefore, it is vital that azoospermic cases with highly-elevated plasma FSH and LH levels be excluded from separate testicular biopsy as they are not suitable cases for conventional treatments. The findings of this study may support the relationship between the plasma levels of FSH and LH, with testicular pathology.

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Conflict of interest

None declared.

References

1. Esmaeilzadeh S, Delavar MA, Zeinalzadeh M, Mir MR. Epidemiology of infertility: a population-based study in Babol, Iran. *Women Health*. 2012;52(8):744-754.
2. De Kretser DM, Baker HW. Infertility in men: recent advances and continuing controversies. *J Clin Endocrinol Metab*. 1999 Oct;84(10):3443-3450.
3. Kumar N, Singh AK. Trends of male factor infertility, an important cause of infertility: A review of literature. *J Hum Reprod Sci*. 2015 Oct-Dec;8(4):191-196.
4. WHO. Towards more objectivity in diagnosis and management of male infertility. *Int J Androl*. 1987;7 (Suppl):1-53.
5. Matsumiya K, Namiki M, Takahara S, Kondoh N, Takada S, Kiyohara H, et al. Clinical study of azoospermia. *Int J Androl*. 1994 Jun;17(3):140-142.
6. Cocuzza M, Alvarenga C, Pagani R. The epidemiology and etiology of azoospermia. *Clinics (Sao Paulo)*. 2013;68 Suppl 1:15-26.
7. Gudeloglu A, Parekattil SJ. Update in the evaluation of the azoospermic male. *Clinics (Sao Paulo)*. 2013;68 Suppl 1:27-34.
8. Bakhtiari A, Basirat Z, Aghajani Mir M. Sexual dysfunction in men seeking infertility treatment: The prevalence and associations. *Caspian Journal of Reproductive Medicine*. 2015;1(3):2-6.
9. Schuppe HC, Pilatz A, Hossain H, Meinhardt A, Bergmann M, Haidl G, et al. [Orchitis and male infertility]. *Urologe A*. 2010 May;49(5):629-35. PubMed PMID: 20449780. Epub 2010/05/08. *Orchitis und Infertilitat*. ger.
10. Azenabor A, Ekun AO, Akinloye O. Impact of Inflammation on Male Reproductive Tract. *J Reprod Infertil*. 2015 Jul-Sep;16(3):123-129.
11. Jensen TK, Andersson AM, Hjollund NH, Scheike T, Kolstad H, Giwercman A, et al. Inhibin B as a serum marker of spermatogenesis: correlation to differences in sperm concentration and follicle-stimulating hormone levels. A study of 349 Danish men. *J Clin Endocrinol Metab*. 1997 Dec;82(12):4059-4063.
12. Andersson AM, Jorgensen N, Frydelund-Larsen L, Rajpert-De Meyts E, Skakkebaek NE. Impaired Leydig cell function in infertile men: a study of 357 idiopathic infertile men and 318 proven fertile

- controls. *J Clin Endocrinol Metab.* 2004 Jul;89(7):3161-3167.
13. O'Donnell L, Stanton P, de Kretser DM. Endocrinology of the Male Reproductive System and Spermatogenesis. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, et al., editors. *Endotext*. South Dartmouth MA: MDTText.com, Inc.; 2000.
14. Dohle GR, Elzanaty S, van Casteren NJ. Testicular biopsy: clinical practice and interpretation. *Asian J Androl.* 2012 Jan;14(1):88-93.
15. Bushnik T, Cook JL, Yuzpe AA, Tough S, Collins J. Estimating the prevalence of infertility in Canada. *Hum Reprod.* 2012 Mar;27(3):738-746.
16. Caroppo E, Colpi EM, Gazzano G, Vaccalluzzo L, Scropo FI, D'Amato G, et al. Testicular histology may predict the successful sperm retrieval in patients with non-obstructive azoospermia undergoing conventional TESE: a diagnostic accuracy study. *J Assist Reprod Genet.* 2017 Jan;34(1):149-154.
17. Yang HL, Shao XJ, Zhu YY, Wu WL. [Predictive factors of testicular sperm extraction in men with non-obstructive azoospermia]. *Zhonghua Nan Ke Xue.* 2016 May;22(5):462-466.
18. Bergmann M, Behre HM, Nieschlag E. Serum FSH and testicular morphology in male infertility. *Clin Endocrinol (Oxf).* 1994 Jan;40(1):133-136.
19. Yildirim ME, Koc A, Kaygusuz IC, Badem H, Karatas OF, Cimentepe E, et al. The association between serum follicle-stimulating hormone levels and the success of microdissection testicular sperm extraction in patients with azoospermia. *Urol J.* 2014 Jul-Aug;11(4):1825-1828.
20. Gnessi L, Fabbri A, Spera G. Gonadal peptides as mediators of development and functional control of the testis: an integrated system with hormones and local environment. *Endocr Rev.* 1997 Aug;18(4):541-609.
21. de Kretser DM, Kerr JB, Paulsen CA. Evaluation of the ultrastructural changes in the human sertoli cell in testicular disorders and the relationship of the changes to the levels of serum FSH. *Int J Androl.* 1981 Apr;4(2):129-144.
22. Babu SR, Sadhnani MD, Swarna M, Padmavathi P, Reddy PP. Evaluation of FSH, LH and testosterone levels in different subgroups of infertile males. *Indian J Clin Biochem.* 2004 Jan;19(1):45-49.
23. Nistal M, Jimenez F, Paniagua R. Sertoli cell types in the Sertoli-cell-only syndrome: relationships between Sertoli cell morphology and aetiology. *Histopathology.* 1990 Feb;16(2):173-180.
24. Turek PJ, Kim M, Gilbaugh JH, 3rd, Lipshultz LI. The clinical characteristics of 82 patients with Sertoli cell-only testis histology. *Fertil Steril.* 1995 Dec;64(6):1197-1200.
25. Micic S. The effect of the gametogenesis on serum FSH, LH and prolactin levels in infertile men. *Acta Eur Fertil.* 1983 Sep-Oct;14(5):337-340.
26. Weiss DB, Gottschalk-Sabag S, Zukerman Z, Bar On E, Kahana Z. [Follicle-stimulating hormone in azoospermia in prediction of spermatogenic patterns]. *Harefuah.* 1998 Sep;135(5-6):169-175, 256.