



Relationship of gonadotropin hormone levels with testicular dysfunction in patients suffered from varicocele before and after stimulation by gonadotropin releasing hormone

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ABSTRACT

Introduction: Since the early diagnosis and treatment of varicocele during adolescence can help in reducing the risk of future infertility, finding an appropriate indication is very important in order to avoid unnecessary treatment as well as avoid future infertility. Currently, surgery indications for varicocele in adolescents are including high-grade varicocele and testicular volume loss which there is no relation between these cases and semen parameters.

Objectives: In the current study, the relationship of gonadotropin hormone levels was compared to testicular dysfunction in varicocele patients before and after stimulation by gonadotropin releasing hormone (GnRH).

Patients and Methods: Around 60 patients between 18-30 years old were divided into two groups; patients with normal semen analysis (A) and patients with abnormal semen analysis (B). Hormonal analysis including the measurement of basal luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) (bLH and bFSH) and also measurements of LH and FSH after GnRH stimulation test (sLH and sFSH) were carried out. Data were analyzed using t test by SPSS statistical software.

Results: Of 60 patients, 30 patients had normal semen (group A) and 30 patients had abnormal semen parameters (group B). The bLH in group A was lower than group B and bFSH in group A were more than group B, but there was not a significant difference between them. sLH levels were significantly higher in group A than those of group B and sFSH levels in group B were greater than group A. However the difference was not significant.

Conclusion: Testicular volume loss is not suitable criteria for prediction of testicular dysfunction; GnRH stimulation test has a potential for identifying patients with varicocele that are requiring prophylaxis surgery. Increasing serum levels of LH after stimulation by GnRH can also be applied as a suitable index for prophylaxis surgery in varicocele patients to prevent infertility in future.

Implication for health policy/practice/research/medical education:

Testicular volume loss is not suitable criteria for prediction of testicular dysfunction. Gonadotropin releasing hormone stimulation test may be useful to identify patients with varicocele that are requiring prophylaxis surgery.

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Introduction

A varicocele can be defined as an abnormal tortuosity and dilation of the veins of the pampiniform plexus (1). A varicocele results when valves within the veins which run along the spermatic cord prohibit blood from

flowing properly, resulting to swelling of the veins. Some researchers believe that the increased temperature that results from the pooled blood in the blocked veins can decrease sperm count and motility of sperm and increase the proportion of deformed sperms. It may also cause

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pain and testicular atrophy (1-3). History of varicocele in teenagers (11-19 years old) is different from adults. It seems that varicocele is progressing rapidly in adolescents leading to progressive damage to the testis through different pathogenic mechanisms, but it rarely develops after the age of 40 years (4,5). It is found rarely in patients below the age of 10 years, and its incidence increases during puberty, reaching 15% to 20% at the age of 14 to 15 years (6,7), which is similar to that reported in adults (8). Some studies have also reported the prevalence of varicocele to be 18% in teenagers (9). It is reported that more than 77% of the patients suffered from varicocele have experienced failure of growth of one side or two sides of testis (10). Evidence obtained from animal and human studies have proved that varicocele is associated with a time-dependent decline in testicular function (11,12). Varicoceles are known to be the most common correctable cause of infertility in men. Their incidence among infertile men is 20%-40%. Hence, the early diagnosis and treatment of varicocele during adolescence can reduce the risk of future infertility. Only a minority of patients with varicocele will experience fertility problems in adult life if left untreated. Therefore, prophylactic surgery on all adolescents with varicocele would not be necessary. Currently, surgery indications for varicocele in adolescents are including high-grade varicocele and testicular volume loss. Some researchers reported, no relation between these cases and semen parameters (2,3). Finding an appropriate indicator is very important in order to avoid unnecessary treatment and future infertility.

Various attempts have been performed to detect primary parameters involved in testicular disorders in varicocele patients (13,14). The gonadotropin response to the intravenous injection of gonadotropin-releasing hormone (GnRH) has been described as a method of detecting testicular dysfunction in adolescents with varicocele.

Objectives

In the present study, we aimed to study the relationship between gonadotropin hormone levels and testicular dysfunction in varicocele patients before and after stimulation by GnRH.

Materials and Methods

This interventional experimental study was carried out from June to December 2013 in Imam-Ali clinic, Shahrekord University of Medical Sciences, Iran. Around 60 patients between 18-30 years old suffered from varicocele that had at least two semen analysis, were selected by convenience sampling. Data were collected using clinical examination and questionnaire. In addition, hormonal analysis including the measurement of basal LH and FSH (bLH and bFSH) as well as the measurement of LH and FSH after GnRH stimulation test (sLH and sFSH) were carried out. At first, the blood sampling of undertreatment group was performed and the amount of bLH and bFSH was detected. Then, 0.1 mg of Buserelin (superfact; a GnRH agonist) was prescribed by nasal

spray form and after 60 minutes, then blood samples was provided and the levels of luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) were measured.

In the next stage, patients were assigned into two groups regarding to the semen analysis parameters in accordance with WHO criteria as follows; patients with normal semen analysis (A) and patients with abnormal semen analysis (B). The results of hormonal tests were compared between these two groups.

Ethical issues

1) The research followed the tenets of the Declaration of Helsinki; 2) Informed consent was obtained, and they were free to leave the study at any time and 3) The research was approved by the ethical committee of Shahrekord University of Medical Sciences (ethical cod#91-12-17).

Statistical analysis

Data were analyzed using descriptive statistical tests by SPSS software and *t* test was applied. *P* value less than 0.05 was considered as significant.

Results

Around 60 patients participated in the current study and had an age range of 18-30 years old years. All patients were suffered from grade three varicocele in the left side. Around 30 patients presented normal semen analysis (group A) and 30 patients presented abnormal semen analysis (group B).

The amounts of FSH before and after stimulation test in groups A and B are presented in Table 1. The level of base FSH (bFSH) in group A was 3.21 ± 2.3 IU/L and after intervention (stimulation) the level of sFSH was recorded as 5.82 ± 5.43 IU/L. There was a significant difference between these two levels ($P < 0.05$). The serum level of base FSH in group B was 2.56 ± 1.86 IU/L and after intervention it was recorded as 7.45 ± 5.36 IU/L, which was showed a significant difference ($P < 0.016$). Moreover, there was not any significant difference in bFSH (baseline FSH) of two groups A and B ($P = 0.88$).

The amounts of LH before and after stimulation test in groups A and B are presented in Table 2. The basic level of LH in group A was 5.17 ± 2.37 IU/L and it was found 23.13 ± 15.07 IU/L after intervention. The change range of LH in group A before and after stimulation obtained 17.95 ± 14.94 ($P < 0.001$). The basic level of LH in group B was 5.69 ± 2.46 IU/L and it was found to be 17.8 ± 8.69 IU/L after intervention. The changes of LH in group B obtained 12.1 ± 8.32 that was significant ($P < 0.001$). As

Table 1. The amounts (mean \pm SD) of FSH before and after stimulation test and changes range in groups A and B

Group	bFSH IU/L	sFSH IU/L	Changes range IU/L	<i>P</i> value
A	3.21 \pm 2.3	5.82 \pm 5.43	4.035 \pm 2.6	<0.001
B	2.56 \pm 1.86	7.45 \pm 5.36	5.96 \pm 2.8	<0.016
<i>P</i> value			0.88	

Table 2. The amounts (mean \pm SD) of LH before and after stimulation test and changes range in groups A and B

Group	bLH IU/L	sLH IU/L	Changes range IU/L	P value
A	5.17 \pm 2.37	23.13 \pm 15.07	17.95 \pm 14.94	<0.001
B	5.69 \pm 2.46	17.8 \pm 8.69	12.1 \pm 8.32	<0.016
P value	0.4			

presented in Table 2 no significant difference in basic levels of LH of two groups A and B was detected ($P=0.4$). The results showed no significant difference in FSH changes of two groups A and B ($P=0.88$). Accordingly, no significant difference in changes rate of LH between two groups was detected ($P=0.4$).

Discussion

Varicoceles are the most common curable abnormality in infertile men which may cause damage to the movement, morphology and sperm count (2). It is accepted in the researches that early diagnosis and surgery of varicocele in adolescents in comparison with untreated group can improve the viable sperms as well as the testicular volume (15-17). The gonadotrophins response to GnRH has been accepted as a diagnosis method of testicular function disorders in adolescent with varicocele (13).

As expected theoretically, the rate of LH and FSH increased in response to GnRH stimulation during the present study. Comparing patients with normal semen analysis (A) and abnormal semen analysis (B), only FSH changes showed significant difference.

The efficacy of the base levels of gonadotropins and their levels after hormonal stimulation tests to predict testicular damage due to varicocele has been proposed in several studies. Kass et al investigated the gonadotropins response to intravenous injection of LHRH (luteinizing hormone-releasing hormone) in 53 male adolescents (11-17 years old) suffered from varicocele grade 2-3. The authors concluded that gonadotropin response to GnRH can be considered as a diagnostic indicator for testicular dysfunction in adolescents with varicocele. They suggested that LHRH stimulating test must be considered as a part of routine investigations of varicocele in adolescent (13). Also, gonadotropin-releasing hormone stimulation test was performed on 104 adolescent males with a unilateral left varicocele. The results showed an increase in the levels of LH and FSH in response to GnRH in adolescents and adults with varicocele (13). In another study performed on 76 adolescents with varicocele (17.5 \pm 1 years old), After stimulating tests by intravenous injection of GnRH (100 μ g) they observed that LH and FSH dosage could determine the risk of infertility with or without GnRH stimulating test (3). A study was also performed on 15 adolescents in the range of 10-17 years old suffered from left sided varicocele 2-3 grade. They investigated the testicular volume as well as the gonadotropins response to LHRH stimulating test. Data were compared with the results of histological tests provided by two-sided

testicular biopsies. Differences in the sizes of testes were not significant between left and right side- testes and these findings had not any clearly relationship with unnatural histology findings. A high relationship between testes damages and increasing response of gonadotropins to LHRH stimulation was detected (18). The reduction of testes sizes did not show any relationship with testes damages (18).

Some researchers investigated the gonadotropin response to intravenous injection of GnRH (100 g) as well as the response of testosterone to HCG daily during three days before and three months after varicocelectomy in five male adolescents (17-20 years old) with left- sided varicocele. The authors reported that the gonadotropin response increased after GnRH stimulation but it decreased after varicocelectomy (19).

In another study, a group of researchers indicated that the size of testes is not a suitable criteria to diagnose testicular disorders in adolescents. They observed a remarkable increase in the bFSH level and LH, FSH levels after stimulating by GnRH in patients suffered from varicocele with semen liquid disorders. They concluded that only FSH and LH dosages could be useful in order to diagnose patients with high risk of infertility (3).

Increased LH response to GnRH stimulation test is associated with dysfunction of Leydig cells, whereas, the increase of FSH levels is related to dysfunction of Sertoli cells (3). In most adults, the normal response to intravenous injection of GnRH (100 μ g) must be increased LH levels 10 IU/L and FSH levels 2 IU/L (20). In the present study, FSH showed an increase of 4.035 \pm 2.6 IU/L and 5.96 \pm 2.8 IU/L in varicocele patients with natural semen analysis (A) and abnormal semen analysis (B), respectively. The LH showed an increase of 17.95 \pm 14.94 IU/L in groups A and 17.8 \pm 8.69 IU/L in group B. The above mentioned changes in FSH and LH in response to GnRH stimulation test in this study were higher than the normal ranges reported in resources. In the study of Guarino et al, the levels of FSH after stimulation by GnRH significantly increased, but no significant changes in LH levels was reported (3). In contrast to the above reports, in our study the LH levels increased statistically significant. This can be related to more vulnerable and more susceptible Leydig cells to adverse environmental conditions.

Conclusion

As it was mentioned in the present study, LH and FSH changes in response to GnRH stimulation were more than the natural rates listed in other resources. Thus, it is recommended that the stimulation test can be used for diagnosis of patients with varicocele, particularly in cases that there is a diagnostic ambiguity. According to the significant changes of LH in response to GnRH in the group with abnormal analysis of semen compared with the normal group, this test can be used as an indication for screening in varicocele patients requiring to prophylaxis surgery for the prevention of infertility in addition of traditional methods such as testicular volume loss and

high grade varicocele.

Limitations of the study

Low proportion of patients was a limitation for our study. It is necessary to reinvestigate, the data of our study with larger multi-centric studies.

Authors' contribution

MS; study design, preparation of manuscript, final revision, and data interpretation. SAF; study design, manuscript edition, and final revision. MAF; data gathering, data interpretation, and manuscript preparation.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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