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ORIGINAL ARTICLE

Effect of Varicocelectomy on Serum FSH and LH Levels for Patients with Varicocele: a Systematic Review and Meta-analysis.

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Abstract Varicocelectomy can improve the function of testicular Leydig cell for patients with varicocele. We carried out a systematic review and meta-analysis to assess effect of varicocelectomy on serum FSH and LH levels for patients with varicocele. A literature review was performed to identify all published randomized preoperation-postoperation clinical trials of assessing serum FSH and LH levels before and after varicocelectomy. The search included the following databases: PUBMED and EMBASE. The reference lists of retrieved studies were also investigated. A systematic review and meta-analysis were conducted. Five studies were selected from 149 studies, including 312 patients. The meta-analysis showed that serum FSH level (95% confidence interval 0.19–0.77, $P = 0.001$) and serum LH level (95% confidence interval 0.25–0.91, $P = 0.0005$) were higher preoperation than postoperation. Serum FSH level decreased by 0.48 ng/dL after varicocelectomy. The mean decrease of the serum FSH was from 0.1 to 4.8 ng/dL. And serum LH decreased by 0.58 ng/dL. The mean decrease of the serum LH was from 0.2 to 2.1 ng/dL. This meta-analysis proves that varicocelectomy perhaps can decrease serum FSH and LH levels in patients with varicocele. And it might be related to the improvement of the function of Leydig cell. But it remains to need a large-scale multicenter randomized controlled study to be further confirmed.

Keywords FSH · LH · Leydig cell · Varicocele · Varicocelectomy

Introduction

Varicocele is a common problem in reproductive medicine practice. A varicocele is identified in 15% of healthy men and up to 35% of men with primary infertility [1]. In recent years, many studies have demonstrated data regarding the etiology and pathophysiologies of varicocele in different point of views [2] and its influence on spermatogenesis and the reproductive hormonal axis. Varicoceles are a major cause of impaired spermatogenesis and the most common correctable cause of male infertility [3]. Treatment of varicocele by varicocelectomy can improve the potential of fertility [4]. In recent years, there were many studies that described the links of varicocele and testosterone production. We had known that varicocele could impair testicular Leydig cell function with a consequential decrease in testosterone production [5, 6]. Many studies report that varicocelectomy can promote the function of Leydig cells by increasing testosterone. For example, Li F had carried a meta-analysis that showed that mean serum testosterone level increased after varicocelectomy [7]. However, varicocele and varicocelectomy also can result in the changes of serum FSH and LH levels, but the reasons are not clearly identified. Some studies found that the levels of serum FSH and LH were unchanged after varicocelectomy. Others noted that varicocelectomy could decrease the serum FSH and LH levels.

The goal of the present study was to perform a meta-analysis to assess the effect of varicocelectomy on serum FSH and LH levels, which may further explore the potential mechanism of varicocele and its effect on infertility.

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Material and Methods

Inclusion Criteria

Clinical trials that met the following criteria were included: (1) a study design that included varicocelectomy for varicocele; (2) the study provided accurate efficacy and safety data that could be analyzed, including the total number of subjects and the values of each index; and (3) the full text of the study could be accessed. If these inclusion criteria were not met, then the study was excluded from the analysis.

Search Strategy

MEDLINE (from 1974 to August 2015), EMBASE (from 1974 to August 2015), and the reference lists of retrieved studies were searched to identify clinical trials that referred to the effect of varicocelectomy for the levels of serum FSH and LH. The following search terms were used: FSH, LH, Leydig cell, varicocele, and varicocelectomy.

Trial Selection

When the same study was published in various journals or in different years, the most frequently cited one was used for the meta-analysis. If the same group of researchers studied a group of subjects with multiple experiments, then each study was included. Together, we discussed each of the clinical trials that were included and excluded studies that either failed to meet the inclusion criteria or could not be agreed upon by the authors. A flow diagram of the study selection process is presented in Fig. 1.

Quality Assessment

The methodological quality of each study was assessed according to how patients were allocated to the arms of the study, the concealment of allocation procedures, blinding, and the data loss due to attrition. The studies were then classified qualitatively according to the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [8]. Based on the quality-assessment criteria, each study was rated and assigned to one of the three following quality categories: A: if all quality criteria were adequately met, the study was deemed to have a low risk of bias; B: if one or more of the quality criteria was only partially met or was unclear, the study was deemed to have a moderate risk of bias; or C: if one or more of the criteria were not met, or not included, the study was deemed to have a high risk of bias. Sensitivity analyses were then performed on the basis of whether these quality factors were adequate, inadequate, or unclear. Differences were resolved by discussion among the authors.

Data Extraction

The following information was collected: (1) the name of the first author and the publication year; (2) the study design and sample size; (3) the source of the patients; (4) the surgical approach; (5) the grade of varicocele; (6) the age of patients; (7) the data including the levels of serum FSH and LH preoperation; and (8) the data including the levels of serum FSH and LH postoperation.

Statistical Analysis

The meta-analysis of comparable data was carried out using Review Manager 5.0.0. Statistical significance was set at a P value less than 0.05. Statistical heterogeneity of studies was investigated using I-squared statistics.

Results

Characteristics of Individual Studies

The database search found 149 articles that could potentially have been included in our meta-analysis. Based on the inclusion and exclusion criteria, 111 articles were excluded after a simple reading of the titles and abstracts of the articles. Twenty-nine articles were excluded because they were not randomized preoperation-postoperation clinical trials. Four articles from nine articles had to be excluded from review because they do not include the data of serum FSH and LH levels at the same time. In all, five articles [9–13] with nine clinical trials were included in the analysis: preoperation and postoperation, respectively. The clinical trials in these articles had been conducted in Japan, Egypt, Europe, and Taiwan. The number of patients included in each of the nine studies was relatively small, varying between 31 and 103 patients. The baseline characteristics of the studies included in our meta-analysis are listed in Table 1.

Quality of Individual Studies

The studies in the analysis were clinical trials. The level of quality of each identified study was B (Table 2). The funnel plot provided a qualitative estimation of publication bias of the studies, and no evidence of bias was found. (Fig. 2).

The Changes of Serum FSH Level Preoperation and Postoperation

Nine clinical trials included the data of the levels of serum FSH changes representing a cohort of 312 participants (312 in the preoperation and 312 postoperation). The pooled estimate of SMD was 0.48, and the 95% CI was 0.19–0.77. This

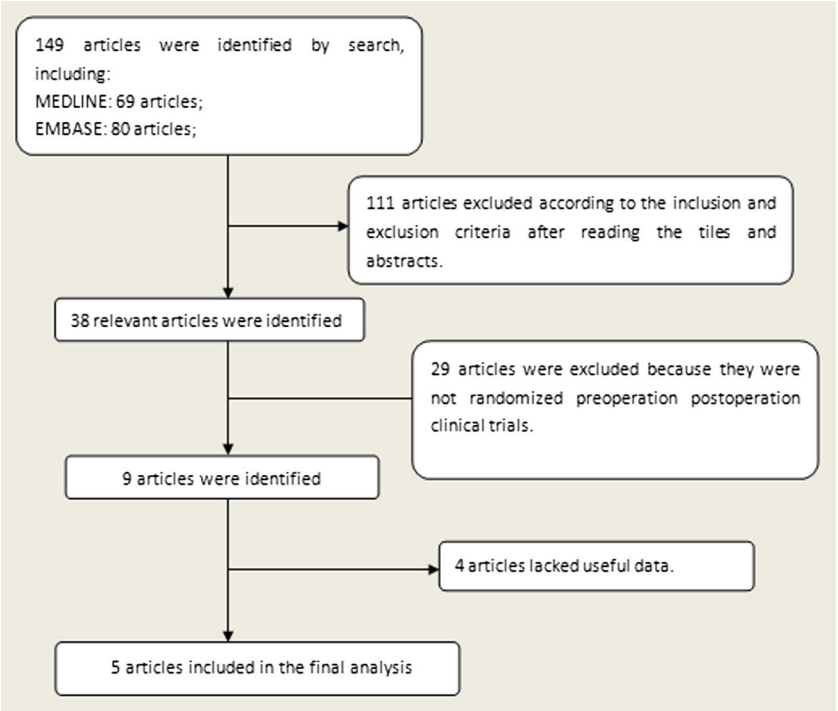

Fig. 1 The flow diagram of the study selection

result supports the assertion that the level of serum FSH was higher preoperation than postoperation ($P < 0.001$). The mean decrease of the serum FSH was from 0.1 to 4.8 ng/dL (Fig. 3).

The Changes of Serum LH Level Preoperation and Postoperation

Nine clinical trials included the levels of serum LH changes data representing a cohort of 312 participants (312 in the preoperation and 312 postoperation). According to our analysis, no heterogeneity was found among the trials, and a fixed-effects model was thus chosen for the analysis. The pooled estimate of SMD was 0.58, and the 95% CI was 0.25–0.91. This result supports the assertion that the levels of serum LH was higher preoperation than postoperation ($P < 0.0005$). The mean decrease of the serum LH was from 0.2 to 2.1 ng/dL. (Fig. 4).

Kaneko T [14] carried out microsurgical varicocelectomy on nine boys and 19 men. They found that catch-up growth of

Table 1 Study and patient characteristics

Study	Age (years)	Country	No. patients	Varicocele Grade (I II III)	Follow-up (months)	Surgical approach
Chen SS 2011	34.7–35.2	Taiwan	35	8/35(I) 17/35(II) 109(III)	6 months	Subinguinal/microsurgical varicocelectomy.
Zohdy W 2010	Group I 34 ± 5.8 Group II 33.1 ± 5.9	Egypt	103	NA	6 months	Microsurgical varicocelectomy.
Reşorlu B 2009	Group I 18–25 Group II 26–35 Group III ≥35	Turkey	96	NA	6 months	Microsurgical/subinguinal varicocelectomy
Onozawa M 2002	34.1 ± 5.1	Japan	31	NA	76.2 months	Subinguinal varicocelectomy
Y Fujisawa M 2001	24–42	Japan	52	13/52(I) 19/52(II) 20/52(III)	6 months	Subinguinal varicocelectomy

NA not available

Table 2 Quality assessment of individual study

Study	Allocation sequence generation	Allocation concealment	Blinding	Calculation of sample size	Statistical analysis	Intention-to-treat analysis	Level of quality
Chen SS 2011	B	B	B	Yes	The paired *t* test	Yes	B
Zohdy W 2010	B	B	B	Yes	The paired *t* test	Yes	B
Reşorlu B 2009	B	B	B	Yes	The paired *t* test	Yes	B
Onozawa M 2002	B	B	B	Yes	The paired *t* test	Yes	B
Fujisawa M 2001	B	B	B	Yes	The paired *t* test	Yes	B

A all quality criteria met (adequate): low risk of bias, *B* one or more of the quality criteria only partly met (unclear): moderate risk of bias, *C* one or more criteria not met (inadequate or not used): high risk of bias

the testis was seen in 62.5% of boys after varicocelectomy. FSH level was significantly lower in boys with catch-up growth than in boys without catch-up growth. Improved sperm concentration was seen in 73.6% of adults after varicocelectomy. FSH level was significantly lower in adults with improved sperm concentration than in patients without improved sperm concentration (in adolescent: catch-up growth (+): 1.5 ± 0.9, catch-up growth (−): 4.0 ± 0.6 $P < 0.01$; in adults: cases of improvement (+): 5.2 ± 6.5, cases of improvement (−): 9.6 ± 8.9 $P < 0.0001$). The serum FSH level might be the relevant predictive parameter for testicular development and function after surgery.

Discussion

Many studies have demonstrated data regarding the etiology and pathophysiologies of varicocele and its influence on spermatogenesis and the reproductive hormonal axis. Also, varicocelectomy might induce a higher probability of pregnancy [12]. The finding of increased serum FSH and LH in infertile men with varicocele has also led to the hypothesis that varicocele result in Leydig cell dysfunction and subsequently to increase the levels of serum FSH and LH. Fujisawa M [13] noted that patients with a low serum level of FSH and LH after varicocelectomy. And Chen SS et al. suggested that the significant predictive factors of successful varicocelectomy in infertile patients was low serum concentration of FSH [9]. Reşorlu B et al. performed a study that suggested that age is not a significant factor for outcomes of surgery and subinguinal microsurgical varicocelectomy in all aged patients that have similar high success rates [11]. Contrary to the findings of those studies, other studies have shown no meaningful difference in serum FSH and LH production with varicocele patients after surgery. T. Mostafa [15] noted that the levels of serum FSH, LH, T hormones, and pregnancy rate (23.3% versus 22.9%) 1 year postoperatively showed no meaningful difference. There are controversies over varicocelectomy for the effect of the levels of serum FSH and LH. So, we carried a meta-analysis that showed that mean serum FSH level after varicocelectomy decreased 0.48 ng/dL (95% confidence interval 0.19–0.77, $P = 0.001$) compared with preoperative level. The mean decrease of the serum FSH was from 0.1 to 4.8 ng/dL. And the level of serum LH decreased 0.58 ng/dL (95% confidence interval 0.25–0.91, $P = 0.0005$). The mean decrease of the serum LH was from 0.2 to 2.1 ng/dL. The levels of serum FSH and LH were higher preoperation than postoperation.

However, the exact mechanism of effect of varicocele on infertility is poorly understood so far. Several hypotheses have been suggested to explain the deleterious effect of varicocele on testis function. The most accepted hypothesis is related to alterations in the testicular thermal environment. The spermatic veins leaving the testicles form a communicating meshwork of veins that produces a counter-current heat-exchange mechanism to cool the arterial blood [16]. This mechanism is eliminated in patients with varicocele, causing elevated scrotal temperatures. Furthermore, spermatic enzyme activity, such as enzyme 5α-reductase (SRD5A), it was decreased in the patients with varicocele. By affecting the conversion of testosterone into 5α-dihydrotestosterone, it may be an important additional mechanism involved in the harmful effect of varicocele in male fertility [17]. This can be reversed after surgery, improving the Leydig cell environment for enzyme activity,

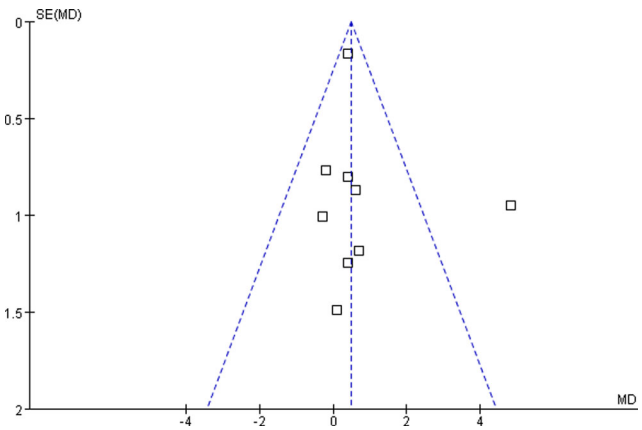

Fig. 2 Funnel plot

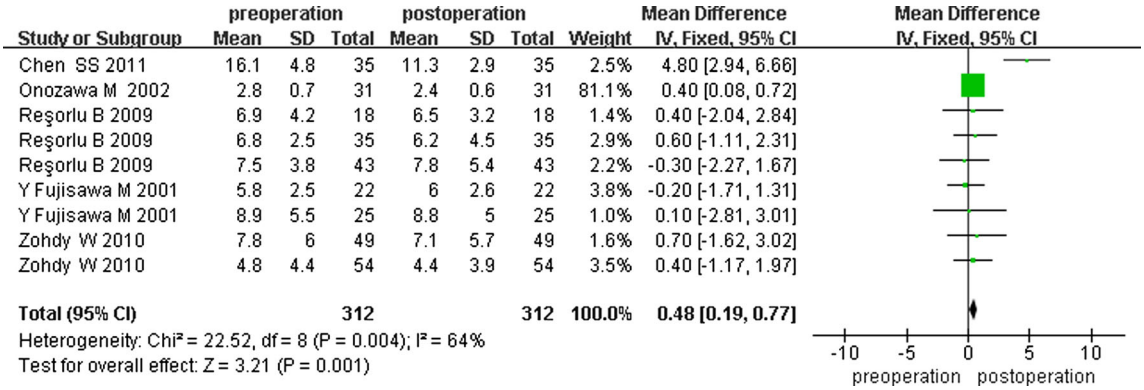

Fig. 3 The serum FSH level preoperation and postoperation

thus leading to a postoperative increase in serum testosterone levels. As we all know, the function of Leydig cell is to produce testosterone, but is controlled by LH. The function of FSH is to promote the beginning of the production of testosterone; LH is to maintain the process. So, we consider that there are correspondence with the changes of serum FSH, LH, and testosterone. It may be involved in function of the hypothalamic–pituitary–gonadal axis. Fuping Li [7] carried an analysis that showed that mean serum testosterone level increased after varicocelectomy. Our meta-analysis showed that the serum FSH and LH levels in patients with varicocele decreased after varicocelectomy. It accords with the mechanism of the negative feedback of the hypothalamic–pituitary–gonadal axis. So, our study perhaps can prove that varicocelectomy can improve the function of Leydig cell in another point of view.

Kaneko T [14] carried out microsurgical varicocelectomy on nine boys and 19 men. They found that catch-up growth of the testis was seen in 62.5% of boys after varicocelectomy. FSH level was significantly lower in boys with catch-up growth than in boys without catch-up growth. Improved sperm concentration was seen in 73.6% of adults after varicocelectomy. FSH level was significantly lower in adults with improved sperm concentration than in patients without improved sperm concentration. So, the serum FSH level might be the relevant predictive parameter for testicular development and function after surgery.

This meta-analysis includes five studies. And the sample sizes were not large. In addition, unpublished studies were not included in the analysis. These factors may have resulted in bias. The major bias was the type of studies was clinical trials. According to the quality-assessment scale that we developed, the quality of individual studies in the meta-analysis was variable. Quality appears to be the main reason for heterogeneity among these studies, and this heterogeneity likely arose from several factors. First, there were important differences in the adequacy of the randomization process, blinding methodology, the use of preoperation-postoperation groups. Second, the study outcomes may have been measured by different methods. Third, the researchers in the trials were different. Finally, potential selection biases could have influenced the homogeneity of the groups, and relatively small sample sizes limited the statistical power for identifying true associations. After the heterogeneity among individual studies is taken into account, this meta-analysis remains crucial for assessing the varicocelectomy for the effect of the levels of serum FSH and LH. More high-quality trails with larger samples are proposed to learn more about the varicocelectomy for the effect of the

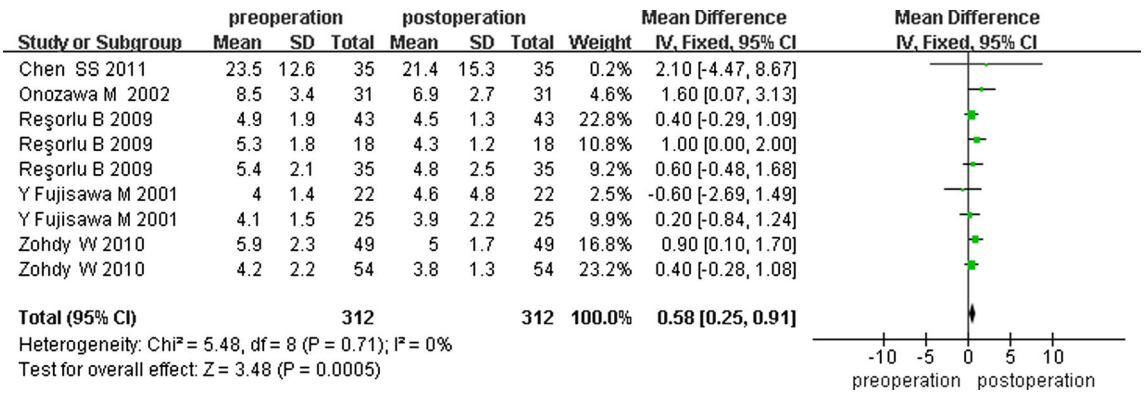

Fig. 4 The serum LH level preoperation and postoperation

levels of serum FSH and LH. The ethical constraints of performing RCTs on the subject is based on the type of selected study. If it is a case-control study, we think that there are ethical constraints because the control group cannot be treated. If it is a self-control study, though there are not significant ethical constraints, we think it still needs be discussed and approved by the ethics committee. And there were not animal studies that had proven the effect on FSH and LH. So, we suggested animal studies should be carried out before performing RCTs on the subject.

Conclusions

This meta-analysis proves that varicocelectomy perhaps can decrease serum FSH and LH levels in patients with varicocele. And it might be related to the improvement of the function of Leydig cell. But it remains to need a large-scale multicenter randomized controlled study to be further confirmed.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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